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(71) Applicant and
(72) Inventor: GORE, Stanley, L. [CA/CA]; 10 Silverbirch Avenue, Toronto, Ontario M4E 3K9 (CA).

(74) Agent: HUGUES, Ivor, M.; Suite 200, 175 Commerce Valley Drive West, Thornhill, Ontario L3T 7P6 (CA).

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(54) Title: COMPOSITIONS AND METHODS FOR INTRANASAL DELIVERY OF ACTIVE AGENTS TO THE BRAIN

(57) Abstract: The present invention relates to a method for delivering at least one active agent to the brain of a mammal. The method comprises administering the at least one active agent to the nasal mucosa of the mammal, wherein the at least one active agent is absorbed through at least one area of nasal epithelium to at least one group of nerve fibers and delivered along at least one neural pathway into the brain of the mammal. The at least one active agent is preferably administered in the form of a composition containing at least one pharmaceutically-acceptable carrier.

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TITLE OF THE INVENTION

COMPOSITIONS AND METHODS FOR INTRANASAL DELIVERY OF ACTIVE AGENTS TO THE BRAIN

FIELD OF THE INVENTION

The present invention relates to compositions and methods for the intranasal delivery of active agents to the brain and is particularly concerned with compositions and methods for the intranasal delivery of active agents to the brain by means of neural pathways.

BACKGROUND OF THE INVENTION

There are limited routes currently available to deliver substances to the brain. The traditional, historical methods and routes of delivery are: (a) the intravascular delivery of substances across the blood-brain and/or blood-cerebrospinal fluid (CSF) barriers and (b) the injection of substances directly into the brain or cerebrospinal fluid.

With respect to the intravascular route across the blood-brain and/or blood-CSF barriers, substances must first be instilled into the bloodstream directly by injection or indirectly by intramuscular injection, absorption through the gastrointestinal (GI) tract, skin or mucous membrane. Then they must travel to the brain, leave the bloodstream, cross the blood-brain and/or blood-CSF barriers and enter the brain matter either directly or indirectly through the CSF. One relevant method is addressed by Hansen P. in United States Patent No. 5,179,079. Substances in the GI tract may be metabolized by the enzymes of the gastric, intestinal or rectal mucosa, the intestinal flora, or the liver (the so-called first-pass effect) before they gain access to the general circulation, thus decreasing their bioavailability. Once in the general circulation, many substances are impermeable to the blood-brain and/or blood-CSF barriers and thus are unable to traverse them. Even if the substances are permeable and are able to traverse the blood-brain and/or blood-CSF barriers, they may affect other parts of the body causing adverse and/or harmful effects, and/or may be taken up by other parts of the body, thereby significantly increasing the dosage amount required to achieve the desired effect on the brain. With respect to the injection of substances directly into the brain or CSF, issues of safety, ease of use and comfort allow this method limited application.

There are also efficacy and safety limitations to the two aforementioned delivery routes.

In addition, administration of substances intravascularly or by direct injection into the brain or CSF does not facilitate selective delivery of the substances solely to those areas of the brain in which the delivery of the substance is desired. As a result, some areas of the brain may be adversely affected by the substance while other areas may not receive a high enough concentration of the substance to achieve the desired effect. For example, healthy areas of the brain may be adversely affected whereas diseased areas may not receive adequate treatment. Consequently, an alternative and/or supplementary route to routes (a) and (b) above is required.

A third route for the delivery of substances to the brain is the transneuronal transport of substances from the nose to the brain via the olfactory neural pathway following intranasal administration. Nasal, transmucosal, transneuronal delivery of substances along the olfactory neuronal pathway to the brain represents not only a different delivery route from route (a) or (b), but also a different method of brain stimulation. With respect to the delivery route, the substances are carried along the olfactory nerve pathway directly to the brain areas innervated by the olfactory nerve and/or directly to the CSF whereby the substances may then diffuse into the brain parenchyma. With respect to brain stimulation, the application of a substance to the olfactory epithelium of the nasal mucosa can result in two modalities of stimulation. First, olfactory receptors can be stimulated by volatile odor molecules. This chemosensory receptor stimulation results in electrical stimulation of the olfactory nerve, with resultant electrical stimulation of the olfactory bulb and related brain centers. Second, the substance can be transported along or within the olfactory nerve and deposited directly into the olfactory bulb and related brain centers and/or directly into the CSF whereby the substance may then diffuse into the olfactory bulb and related brain centers. This nasal, transmucosal, transneuronal delivery of a substance along the olfactory nerve can result in chemical stimulation of brain centers. United States Patent No. 5,624,898 to Frey, II, WH. teaches that certain neurologic therapeutic agents can be applied directly to the olfactory

epithelium of the nasal cavity of a mammal, thereupon absorbed through the olfactory epithelium and transported to the brain by means of the olfactory neural pathway.

There are several disadvantages to the transneuronal transport of substances to the brain via the olfactory neural pathway. The olfactory epithelium, which is high up in the nose, is too inaccessible to be reached by creams, gels or ointments, and thus requires liquids or powders to be deposited in spray or aerosol form. Either odor-chemosensory stimulation of the olfactory epithelium or transneuronal delivery of substances to the brain along the olfactory nerve, or both, activates only a limited number of brain structures because the olfactory nerve has limited innervations to the brain. These innervations include the olfactory bulb and interconnected areas of the brain such as the hippocampal formation, amygdaloid nuclei, nucleus basalis of Meynert, the locus ceruleus, and the brainstem raphe nuclei. As a result, olfactory stimulation has a limited effect on physiology and/or behavior.

Consequently, with respect to drug delivery systems, and in particular with respect to brain stimulation for the purpose of physiological, hormonal or behavioral modulation, an alternative and/or supplementary route to the olfactory neural pathway is required and would be beneficial.

SUMMARY OF THE INVENTION

The present invention provides a method of transneuronal transport of substances from inside of the nose to the brain via nerve pathways, particularly the vomeronasal-terminalis nerve pathway and a composition to effect such transport.

The neural pathway from the nose to the brain and particularly the vomeronasal-terminalis neural pathway provide a direct route from the exterior of the body to the brain which circumvents the systemic circulation and thus the blood-brain and blood-CSF barriers altogether. Substances are transported along anterograde and/or retrograde neural pathways connecting the nose and the brain. This is a very different delivery mechanism from that resulting from the traditional instillation of substances into the nose, whereby they either are absorbed into the bloodstream and travel to different parts of the body, or they chemically stimulate nerve receptors in the nasal mucosa,

with resultant electrical stimulation of nerves leading to the brain. The areas of the brain targeted by nasal, transmucosal, transneuronal transport are also quite different from those reached by transportation across the blood-brain and/or blood-CSF barriers from the circulation.

The neural pathways from the nose to the brain and particularly the vomeronasal-terminalis neural pathway, can be visualized as a transneuronal 'escalator' or 'conveyor belt' from the nose to the brain. The characteristics of the present invention that make transneuronal transport from the nose to the brain possible and unique include, but are not limited to, the following:

1) the nerve pathway from the nose to the brain is one of the shortest in the body;

2) the nerve pathway is uninterrupted by synapses; there is only one axon connecting the nose and the brain;

3) the nerve pathway is unmyelinated in contrast to most nerves in the body;

4) the at least one pharmaceutically-acceptable carrier or vehicle of the present invention for use in combination with at least one active agent, has the unique ability to a) traverse the nasal mucosa and b) facilitate movement of the at least one active agent along and/or within nerve pathways into the brain.

Transneuronal transport from the nose to the brain, particularly along the vomeronasal-terminalis nerves, delivers substances directly and specifically to the diencephalon area (thalamus, hypothalamus, pineal gland, limbic system) as opposed to the global delivery (cerebral cortex, cerebellum, etc.) of blood-brain barrier transport. The ability to target and influence the areas of the brain that are involved in neuroendocrine regulation (hypothalamus, pineal gland) and in initiation of emotions and patterned complex behavior (thalamus, limbic system) has profound consequences in the medical and behavioral sciences.

There are many differences between the application of a substance to the olfactory epithelium as disclosed in the prior art and the application of a substance to areas of the nasal mucosa other than the olfactory epithelium and particularly to the vomeronasal epithelium, as described in this invention: i)

specific vehicle/carrier compositions are disclosed in this invention; ii) transneuronal transport is effected along different nerves, deposited in different brain centers, resulting in different physiologic, behavioral, therapeutic and/or diagnostic effects; iii) if chemosensory stimulation of receptor organs also results from the application of a substance to the nasal mucosa, the type of molecule required for such stimulation (volatile odor molecules as opposed to volatile and non-volatile pheromone molecules), the nerve (olfactory as opposed to vomeronasal-terminalis and/or trigeminal and/or autonomic) and brain centers thereby electrically stimulated are all different for olfactory as opposed to vomeronasal epithelium substance application. Consequently, the resultant physiologic and/or behavioral effects also differ.

It is an object of the present invention to avoid the disadvantages of the prior art methods and compositions for delivering active agents to the brain.

It is another object of the present invention to provide improved and effective delivery of active agents to the brain.

It is another object of the present invention to provide delivery of active agents to the brain by circumventing the blood-brain and/or blood-CSF barriers.

It is another object of the present invention to provide selective delivery of active agents primarily to areas of the brain in which the active agents are required to produce a desired effect.

It is still another object of the present invention to provide a composition that facilitates the absorption of active agents through at least one area of nasal epithelium into at least one group of nerve fibres and along at least one neural pathway into the brain.

It is still another object of the present invention to treat, prevent, and/or diagnose a disease and/or condition in a mammal.

It is still another object of the present invention to initiation and/or modulation of at least one of the physiology, behavior, thoughts, moods or emotions of a mammal.

It is still another object of the present invention to stimulate the brain of a mammal.

It is still another object of the present invention to provide a reduction in the effective dosage amount of active agents required to be administered to a mammal to obtain a desired effect.

It is still another object of the present invention to provide an alternative route of administration for active agents.

It is still another object of the present invention to provide a reduction in the risk to a mammal of contracting needle-transmitted communicable diseases and/or conditions.

These and other objects of the present invention will be apparent to those skilled in the art from reading the following summary of the invention and the preferred embodiments described herein.

In accordance with an aspect of the present invention, there is provided a composition for use in administering at least one active agent to the nasal mucosa of a mammal and delivering the at least one active agent through at least one area of nasal epithelium, to at least one group of nerve fibers, along at least one neural pathway and into the brain of the mammal; the composition comprising: at least one active agent in combination with at least one pharmaceutically-acceptable carrier.

In accordance with another aspect of the present invention there is provided a use of at least one active agent in combination with at least one pharmaceutically-acceptable carrier in the manufacture of a composition for the treatment and/or prevention of a disease and/or condition in a mammal by administering the composition to the nasal mucosa of the mammal, the composition providing for the delivery of the at least one active agent through at least one area of the nasal epithelium, to at least one group of nerve fibers, along at least one neural pathway; and into the brain of the mammal.

In accordance with another aspect of the present invention there is provided a use of at least one active agent in combination with at least one pharmaceutically-acceptable carrier in the manufacture of a composition for the diagnosis of a disease and/or condition in a mammal by administering the composition to the nasal mucosa of the mammal, the composition providing for the delivery of the at least one active agent through at least one area of the

nasal epithelium, to at least one group of nerve fibers, along at least one neural pathway and into the brain of the mammal.

In accordance with another aspect of the present invention there is provided a use of at least one active agent in combination with at least one pharmaceutically-acceptable carrier in the manufacture of a composition for the initiation and/or modulation of at least one of the physiology, behavior, thoughts, moods or emotions of a mammal by administering the composition to the nasal mucosa of the mammal, the composition providing for the delivery of the at least one active agent through at least one area of the nasal epithelium, to at least one group of nerve fibers, along at least one neural pathway and into the brain of the mammal.

In accordance with another aspect of the present invention there is provided a use of at least one active agent in combination with at least one pharmaceutically-acceptable carrier in the manufacture of a composition for stimulating the brain of a mammal by administering the composition to the nasal mucosa of the mammal, the composition providing for the delivery of the at least one active agent through at least one area of the nasal epithelium, to at least one group of nerve fibers, along at least one neural pathway and into the brain of the mammal.

In accordance with another aspect of the present invention there is provided a use of at least one active agent in combination with at least one pharmaceutically-acceptable carrier in the manufacture of a composition for reducing the effective dosage amount of the at least one active agent required to be administered to a mammal to obtain a desired effect relative to the dosage amount of the at least one active agent which would normally be administered by the vascular route to obtain a substantially similar effect, by administering the composition to the nasal mucosa of the mammal, the composition providing for the delivery of the at least one active agent through at least one area of the nasal epithelium, to at least one group of nerve fibers, along at least one neural pathway and into the brain of the mammal.

In accordance with another aspect of the present invention there is provided a use of at least one active agent in combination with at least one pharmaceutically-acceptable carrier in the manufacture of a composition for

reducing the risk to a mammal of contracting at least one needle-transmitted disease and/or condition, by administering the composition to the nasal mucosa of the mammal, the composition providing for the delivery of the at least one active agent through at least one area of the nasal epithelium, to at least one group of nerve fibers, along at least one neural pathway and into the brain of the mammal.

In accordance with another aspect of the present invention there is provided a method of delivering at least one active agent to the brain of a mammal, the method comprising: applying the at least one active agent in combination with at least one pharmaceutically-acceptable carrier to the nasal mucosa, wherein the at least one active agent is absorbed through at least one area of the nasal epithelium to at least one group of nerve fibers and delivered along at least one neural pathway into the brain of the mammal.

In accordance with another aspect of the present invention there is provided a method of treating and/or preventing a disease and/or condition in a mammal, the method comprising: applying the at least one active agent in combination with at least one pharmaceutically-acceptable carrier to the nasal mucosa of the mammal, wherein the at least one active agent is absorbed through at least one area of the nasal epithelium to at least one group of nerve fibers and an effective amount of the at least one active agent is delivered along at least one neural pathway into the brain of the mammal to prevent and/or treat the disease and/or condition.

In accordance with another aspect of the present invention there is provided a method of diagnosing a disease and/or condition of a mammal, the method comprising: applying the at least one active agent in combination with at least one pharmaceutically-acceptable carrier to the nasal mucosa of the mammal, wherein the at least one active agent is absorbed through at least one area of the nasal epithelium to at least one group of nerve fibers and an effective amount of the at least one active agent is delivered along at least one neural pathway into the brain of the mammal to diagnose the disease and/or condition.

In accordance with another aspect of the present invention there is provided a method of initiating and/or modulating at least one of the

physiology, behavior, thoughts, moods or emotions of a mammal, the method comprising: applying the at least one active agent in combination with at least one pharmaceutically-acceptable carrier to the nasal mucosa of the mammal, wherein the at least one active agent is absorbed through at least one area of the nasal epithelium to at least one group of nerve fibers and an effective amount of the at least one active agent is delivered along at least one neural pathway into the brain of the mammal to initiate and/or modulate the at least one of the physiology, behavior, thoughts, moods or emotions.

In accordance with another aspect of the present invention there is provided a method of stimulating the brain of a mammal, the method comprising: applying the at least one active agent in combination with at least one pharmaceutically-acceptable carrier to the nasal mucosa of the mammal, wherein the at least one active agent is absorbed through at least one area of the nasal epithelium to at least one group of nerve fibers and an effective amount of the at least one active agent is delivered along at least one neural pathway into the brain of the mammal to stimulate the brain of the mammal.

In accordance with another aspect of the present invention there is provided a method of reducing the effective dosage amount of at least one active agent required to be administered to a mammal to obtain a desired effect relative to the dosage amount of the at least one active agent which would normally be administered by the vascular route to obtain a substantially similar effect the method comprising: applying the at least one active agent in combination with at least one pharmaceutically-acceptable carrier to the nasal mucosa of the mammal, wherein the at least one active agent is absorbed through at least one area of the nasal epithelium to at least one group of nerve fibers and an effective amount of the at least one active agent is delivered along at least one neural pathway into the brain of the mammal.

In accordance with another aspect of the present invention there is provided a method of reducing the risk to a mammal of contracting at least one needle-transmitted communicable disease and/or condition, the method comprising: applying the at least one active agent in combination with at least one pharmaceutically-acceptable carrier to the nasal mucosa of the mammal, wherein the at least one active agent is absorbed through at least one area of

the nasal epithelium to at least one group of nerve fibers and an effective amount of the at least one active agent is delivered along at least one neural pathway into the brain of the mammal.

In any of the above embodiments of the present invention, the at least one active agent is capable of at least one of delivering itself through the at least one area of the nasal epithelium, delivering itself to the at least one group of nerve fibers, delivering itself along the at least one neural pathway, delivering itself into the brain of the mammal and combinations thereof. The term "active agent" as used herein includes organic and inorganic agents consisting of very soluble agents, freely soluble agents, soluble agents, sparingly soluble agents, slightly soluble agents, very slightly soluble agents and practically insoluble, or insoluble agents. According to Remington: The Science and Practice of Pharmacy, 19th Edition, ed. Alfonso R. Gennaro, Vol. 1, Table 1, p. 195, Mack Publishing Company, Easton, Pennsylvania 18042, the above-mentioned descriptive terms for solubility are defined. Specifically, very soluble means that less than 1 part of solvent is required to dissolve 1 part of solute. Freely soluble means that from 1 to 10 parts of solvent are required to dissolve 1 part of solute. Soluble means that from 10 to 30 parts of solvent are required to dissolve 1 part of solute. Sparingly soluble means that from 30 to 100 parts of solvent are required to dissolve one part of solute. Slightly soluble means that from 100 to 1000 parts of solvent are required to dissolve one part of solute. Very slightly soluble means that from 1000 to 10,000 parts of solvent are required to dissolve 1 part of solute. Practically insoluble, or insoluble means that more than 10,000 parts of solvent are required to dissolve 1 part of solute. Thus, the term "active agent" encompasses agents which readily cross the blood-brain barrier, agents which do not readily cross the blood-brain barrier and agents which cannot cross the blood-brain barrier.

In any of the above embodiments of the present invention, the amount of the at least one active agent administered to the nasal mucosa of the mammal and delivered along the at least one neural pathway and into the brain to achieve a desired effect, is substantially less than the amount of the at least one active agent which would normally be administered to the mammal to be delivered to the brain by the vascular route to achieve a substantially

similar effect. Preferably, the amount of the at least one active agent administered is from about 1% to about 75% of the amount of the at least one active agent which would normally be administered by the vascular route, more preferably from about 1% to about 50% and most preferably from about 1% to about 25%.

In any of the above embodiments of the present invention, the at least one active agent is selected from the group consisting of a therapeutic agent, a prophylactic agent, a diagnostic agent, an agent which stimulates the brain of a mammal, an agent which initiates and/or modulates at least one of the physiology, behavior, thoughts, moods or emotions of a mammal and combinations thereof.

In any of the above embodiments of the present invention, the at least one active agent is selected from the group consisting of at least one component of at least one secretion collected from at least one skin surface of at least one donor mammal, cholinomimetic agents, central nervous system stimulants, sedatives, narcotics, narcotic antagonists, opioids, opiates, NMDA receptor antagonists, anxiolytic agents, anti-depressant agents, analgesics, anti-migraine agents, anti-convulsant agents, anti-obsessional agents, anti-psychotic agents, anti-Parkinsonian agents, anti-mania agents, agents for the treatment of eating disorders, agents for the treatment of Alzheimer's Disease, agents for the treatment of attention deficit disorders, agents for the treatment of learning disorders, agents for the treatment of memory disorders, agents for the treatment of cognitive disorders, hormones, hormone releasing factors, pheromones, vomeropherins, agents which affect the autonomic nervous system, appetite-suppressant agents, libido-modulating agents, mood-modulating agents, vitamins, minerals, infective agents, agents which modify the mammalian genome or any of the biological effects (intracellular or extracellular) which result therefrom, vaccines, intracellular modifiers, contraceptive agents, anti-viral agents, anti-bacterial agents, anti-neoplastic agents, anti-parasitic agents, anti-inflammatory agents, anti-fungal agents, hypnotic agents, anti-emetic agents, tranquilizers, diagnostic agents, agents which modify the natural aging process of a mammal, agents for the diagnosis

and/or treatment of chemical addictions, agents for the treatment of sleep disorders and combinations thereof.

In an embodiment of the present invention, the cholinomimetic agent is a form of nicotine selected from the group consisting of nicotine base, pharmaceutically-acceptable salts thereof, metabolites thereof, analogs thereof, and combinations thereof.

In an embodiment of the present invention, the central nervous system stimulant is selected from the group consisting of caffeine, pharmaceutically-acceptable salts thereof and combinations thereof.

In an embodiment of the present invention, the central nervous system stimulant is selected from the group consisting of ephedrine, pharmaceutically-acceptable salts thereof and combinations thereof.

In an embodiment of the present invention, the hormone is selected from a group consisting of an androstane, an androstene, an estrane, an estrene, a pregnane, a pregnene, pharmaceutically acceptable salts thereof and combinations thereof.

In an embodiment of the present invention, the hormone is selected from the group consisting of a sex hormone, analogs thereof, precursors thereof, metabolites thereof and combinations thereof. Preferably, the sex hormone is selected from the group consisting of an androgen, an estrogen, a progestogen and combinations thereof. Preferably, the androgen is a form of testosterone selected from the group consisting of testosterone, pharmaceutically-acceptable salts thereof and combinations thereof; the estrogen is selected from the group consisting of estradiol, estriol, estrone, pharmaceutically acceptable salts thereof and combinations thereof; and the progestogen is selected from the group consisting of progesterone, pharmaceutically-acceptable salts thereof and combinations thereof. Preferably, the estradiol is 17ß-estradiol. Preferably, the precursor of a sex hormone is selected from the group consisting of delta 4,16-androstadien-3-one, 1,3,5(10),16-estratetraen-3-ol, pharmaceutically-acceptable salts thereof and combinations thereof.

In an embodiment of the present invention, the hormone is selected from the group consisting of a pituitary hormone, a hypothalamic hormone and combinations thereof.

In an embodiment of the present invention, the infective agent is selected from the group consisting of bacteria, viruses and combinations thereof.

In an embodiment of the present invention, the hormone releasing factor is selected from the group consisting of a hypothalamic hormone releasing factor, a pituitary hormone releasing factor and combinations thereof.

In an embodiment of the present invention, the agent which modifies the mammalian genome is selected from the group consisting of DNA, RNA and combinations thereof.

In an embodiment of the present invention, the diagnostic agent is selected from the group consisting of a monoclonal antibody, a polyclonal antibody, a chemical reagent and combinations thereof. Preferably, the diagnostic agent is labeled and the labeling agent is selected from the group consisting of a radioactive agent, an enzymatic agent, a fluorescent agent and combinations thereof.

In an embodiment wherein the labeled diagnostic agent is an antibody, the antibody is labeled by means of a reaction with a second labeled antibody.

In any of the above embodiments of the present invention, the at least one pharmaceutically-acceptable carrier is capable of facilitating at least one of the delivery of the at least one active agent through the at least one area of the nasal epithelium, delivery of the at least one active agent to the at least one group of nerve fibers, delivery of the at least one active agent along the at least one neural pathway, delivery of the at least one active agent to the brain of the mammal and combinations thereof. The at least one pharmaceutically-acceptable carrier may be hydrophilic, lipophilic or a combination thereof and may be in a form selected from the group consisting of a solid, a semi-solid and a liquid. Preferably, the at least one pharmaceutically-acceptable carrier is selected from the group consisting of an oil-water emulsion, a microemulsion, an organogel, phosphatidylcholine, phosphatidylserine, sphingomyelin, a phosphatidylcholine organogel, a lecithin organogel, a lecithin

microemulsion, a vesicle, a micelle, a proliposome, a liposome, a soluble synthetic polymer, a block co-polymer micelle, a microsphere, a microsponge and combinations thereof. Preferably, the at least one pharmaceutically-acceptable carrier is a lecithin organogel base.

In any of the above embodiments of the present invention, the composition is in a form selected from the group consisting of a liquid, a powder, a spray, an aerosol, drops, a cream, a gel, and an ointment.

In an embodiment of the present invention, the at least one active agent is at least one component of at least one secretion collected from at least one skin surface of at least one donor mammal.

In accordance with another aspect of the present invention, there is provided a method of preparing a composition for use in administering at least one active agent to the nasal mucosa of a mammal and delivering the at least one active agent through at least one area of nasal epithelium, to at least one group of nerve fibers, along at least one neural pathway and into the brain of the mammal; the composition comprising: at least one component of at least one secretion collected from at least one skin surface of at least one donor mammal in combination with at least one pharmaceutically-acceptable carrier, wherein the method comprises:

(a) collecting the at least one component of the at least one secretion from the at least one skin surface of the at least one donor mammal,

(b) optionally extracting the at least one component from the collection into a solvent,

(c) optionally purifying the extraction to obtain less than the total complement of components of the at least one secretion,

(d) optionally concentrating the extraction or purification to obtain a concentrated solution of the at least one component,

(e) optionally adding at least one additional active agent to the extraction, purification or concentration, and

(f) mixing the collection, extraction, purification, concentration or combination with the at least one pharmaceutically-acceptable carrier to obtain the composition. Preferably, the at least one component is selected from the group consisting of volatile components, non-volatile components and

combinations thereof. Preferably, the at least one secretion is selected from the group consisting of apocrine gland secretions, eccrine gland secretions, sebaceous gland secretions and combinations thereof. Preferably, the at least one skin surface is selected from the group consisting of the upper lip, at least one of the axillae, the perineum, the inside of at least one of the thighs, the urethra, the vagina, the penis and combinations thereof. Preferably, the at least one secretion is collected following intercourse, self-stimulation or physical exercise. Preferably, the collection is accomplished by wiping the at least one skin surface with an absorbent means. The absorbent means may include but is not limited to, a cotton ball, a cotton swab, gauze (preferably non-woven) or the like. Preferably, the absorbent means is pre-wetted with the solvent. Preferably, the solvent has both hydrophilic and hydrophobic properties. Preferably the solvent is a substituted or un-substituted lower chain alcohol having from 1 to 6 carbon atoms. Preferably, the solvent is selected from the group consisting of isopropyl alcohol, ethyl alcohol and combinations thereof. In one instance, the absorbent means containing the at least one component is immersed in the solvent to extract the at least one component from the collection into the solvent to obtain a solution. In another instance, the absorbent means containing the at least one component is immersed in the at least one pharmaceutically-acceptable carrier to extract the at least one component from the collection into the at least one pharmaceutically acceptable carrier to obtain the composition. Preferably, the absorbent means containing the at least one component is immersed in the solvent or in the at least one pharmaceutically-acceptable carrier for at least about one hour, preferably for between about 12 to about 24 hours. Preferably, the at least one additional active agent is an agent which has a physiological and/or behavioural effect on the brain of a mammal.

In an embodiment of the present invention wherein the at least one active agent is at least one component of at least one secretion collected from at least one skin surface of at least one donor mammal, the at least one pharmaceutically-acceptable carrier is a lecithin organogel. Preferably, the composition is administered to the nasal mucosa of at least one recipient mammal. In one instance, the at least one donor mammal is a different

individual from the at least one recipient mammal. In yet another instance, the at least one donor mammal and the at least one recipient mammal are of opposite sex and are heterosexual. In still another instance, the at least one donor mammal and the at least one recipient mammal are of the same sex and are homosexual.

In an embodiment of the present invention wherein the at least one active agent is at least one component of at least one secretion collected from at least one skin surface of at least one donor mammal, the composition is useful in initiating and/or modulating at least one of the physiology, thought, mood, emotion or behavior of at least one recipient mammal. The terms "physiology", "thought", "mood", "emotion" and "behavior" as used herein may be sexual and/or non-sexual. The term "behavior" as used herein includes simple behavior, patterned complex behavior and combinations thereof. The term "simple behavior" as used herein includes anxiety, fear, aggression, rage, fight or flight response and combinations thereof. The term "patterned complex behavior" as used herein includes alerting and/or energizing a physical and/or intellectual state, sexual arousal, sexual attraction, addiction, sociability, happiness, euphoria, relaxation, mellowing, and combinations thereof.

In an embodiment of the present invention wherein the at least one active agent is at least one component of at least one secretion collected from at least one skin surface of at least one donor mammal, the composition is useful to elicit at least one of an energizing effect, an alerting sensation, an increase in sexual awareness, an increase in sexual arousal and combinations thereof in at least one recipient mammal.

In an embodiment of the present invention wherein the at least one active agent is at least one component of at least one secretion collected from at least one skin surface of at least one donor mammal, the composition is useful in eliciting a sexual arousal response in at least one recipient mammal.

In an embodiment of the present invention wherein the at least one active agent is at least one component of at least one secretion collected from at least one skin surface of at least one donor mammal, the composition is useful

in treating, preventing, aborting and/or reducing the severity of acute anxiety attacks with obsessional elements in at least one recipient mammal.

In an embodiment of the present invention wherein the at least one active agent is at least one component of at least one secretion collected from at least one skin surface of at least one donor mammal, the composition is useful in the treatment of insomnia in at least one recipient mammal.

In an embodiment of the present invention wherein the at least one active agent is at least one component of at least one secretion collected from at least one skin surface of at least one donor mammal wherein the at least one donor and recipient mammals are of the opposite sex and are heterosexual, the composition is useful to elicit at least one pleasurable mood in the at least one recipient mammal wherein the at least one pleasurable mood is selected from the group consisting of alerting, sexual arousal, relaxation, energizing, increased creativity, enhanced pleasurable sensations and responses during periods of intimacy and combinations thereof.

In an embodiment of the present invention wherein the at least one active agent is at least one component of at least one secretion from at least one skin surface of at least one donor mammal wherein the at least one donor mammal is selected from the group consisting of a male, a female and combinations thereof, the composition is useful to modulate the menstrual cycle of at least one female recipient mammal.

In an embodiment of the present invention wherein the at least one active agent is at least one component of at least one secretion collected from at least one skin surface of at least one donor mammal wherein the at least one donor mammal is selected from the group consisting of a male, a female and combinations thereof, the composition is useful to modulate at least one symptom in at least one female recipient mammal wherein the at least one symptom is associated with at least one syndrome selected from the group consisting of pre-menstrual syndrome, pre-menopausal syndrome, menopausal syndrome, post-menopausal syndrome and combinations thereof.

In an embodiment of the present invention wherein the at least one active agent is at least one component of at least one secretion collected from at least one skin surface of at least one donor mammal wherein the at least one

donor mammal is selected from the group consisting of a male, a female and combinations thereof, the composition is useful to modulate at least one symptom of andropause in at least one male recipient mammal.

In an embodiment of the present invention wherein the at least one active agent is at least one component of at least one secretion collected from at least one skin surface of at least one mammal wherein the at least one donor and recipient mammals are of the same sex and are homosexual, the composition is useful to elicit at least one pleasurable mood in the at least one recipient mammal wherein the at least one pleasurable mood is selected from the group consisting of alerting, sexual arousal, relaxation, energizing, increased creativity, enhanced pleasurable sensations and responses during periods of intimacy and combinations thereof.

In any of the above embodiments of the present invention wherein the at least one active agent is at least one component of at least one secretion collected from at least one skin surface of at least one mammal, the composition may further comprise at least one additional active agent which has a physiological and/or behavioral effect on the at least one mammal. Preferably, the at least one additional active agent is selected from the group consisting of a hormone, a libido-enhancing agent, a sexual performance enhancing agent, a mood-modulating agent, a central nervous system stimulating agent, a cholinomimetic agent and combinations thereof. Preferably, the central nervous system stimulating agent is selected from the group consisting of caffeine, ephedrine, pharmaceutically-acceptable salts thereof and combinations thereof. Preferably, the cholinomimetic agent is a form of nicotine selected from the group consisting of nicotine base, pharmaceutically acceptable salts thereof, metabolites thereof, analogs thereof, and combinations thereof. Preferably, the form of nicotine is present in the composition in an amount ranging between about 0.001% and about 5.0% (w/w), more preferably ranging between 0.05% and about 1.0% (w/w) and most preferably when the composition is in unit dosage form, ranging between about 0.05 mg and about 1.5 mg per dosage unit. Preferably, the hormone is selected from the group consisting of an androstane, an androstene, an estrane, an estrene, a pregnane, a pregnene, pharmaceutically acceptable salts thereof

and combinations thereof. Preferably, the hormone is selected from the group consisting of a sex hormone, an analog thereof, a precursor thereof, a metabolite thereof, and combinations thereof. Preferably, the sex hormone is selected from the group consisting of an androgen, an estrogen, a progestogen and combinations thereof. Preferably, the androgen is a form of testosterone selected from the group consisting of testosterone, pharmaceutically acceptable salts thereof and combinations thereof. Preferably, the form of testosterone is present in the composition in an amount ranging between about 0.001% and about 10.0% (w/w) and more preferably between about 0.1% and about 5.0% (w/w). When the composition is in dosage unit form, the amount of the form of testosterone per dosage unit ranges between about 0.05 mg and about 5 mg. Preferably, the estrogen is selected from the group consisting of estradiol, estriol, estrone, pharmaceutically acceptable salts thereof and combinations thereof. Preferably, the estradiol is 17ß-estradiol. Preferably, the 17ß-estradiol is present in the composition in an amount ranging between about 0.000001% and about 0.01% (w/w) and more preferably between about 0.00001% and about 0.0005% (w/w). When the composition is in dosage unit form, the amount of 17ß-estradiol per dosage unit ranges between about 0.05 µg and about 1 µg. Preferably, the progestogen is selected from the group consisting of progesterone, pharmaceutically-acceptable salts thereof and combinations thereof. Preferably, the precursor of a sex hormone is selected from the group consisting of delta 4,16-androstadien-3-one, 1,3,5(10),16-estratetraen-3-ol, pharmaceutically acceptable salts thereof and combinations thereof. When the composition is in dosage unit form, the amount of delta 4,16-androstadien-3-one and/or 1,3,5(10),16-estratetraen-3-ol per dosage unit ranges between about 0.1 nmoles and about 100 nmoles, preferably between about 0.5 nmoles and about 20 nmoles.

In an embodiment of the present invention wherein the at least one active agent is at least one component of at least one secretion collected from at least one skin surface of at least one donor mammal in combination with at least one additional active agent, the at least one additional active agent is selected from the group consisting of an androstane or an androstene,

preferably delta 4,16-androstadien-3-one, an estrane or an estrene, preferably 1,3,5(10),16-estratetraen-3-ol, pharmaceutically acceptable salts thereof and combinations thereof. Preferably, the composition is in dosage unit form and the amount of delta 4,16-androstadien-3-one and/or 1,3,5(10),16-estratetraen-3-ol per dosage unit ranges between about 0.1 nmoles and about 100 nmoles, preferably between about 0.5 nmoles and about 20 nmoles.

In an embodiment of the present invention wherein the at least one active agent is at least one component of at least one secretion collected from at least one skin surface of at least one donor mammal in combination with at least one additional active agent, the at least one additional active agent is a pregnane or pregnene.

In an embodiment of the present invention, the at least one active agent is a form of nicotine selected from the group consisting of nicotine base, pharmaceutically-acceptable salts thereof, metabolites thereof, analogs thereof, and combinations thereof. Preferably, the at least one pharmaceutically-acceptable carrier is a lecithin organogel. Preferably, nicotine is present in the composition in an amount ranging between about 0.001% and about 5.0% (w/w) and more preferably between about 0.05% and about 1.0% (w/w). Preferably, the composition is in dosage unit form and the amount of nicotine per dosage unit ranges between about 0.05 mg and about 1.5 mg.

In an embodiment of the present invention wherein the at least one active agent is a form of nicotine, the composition may further comprise at least one additional active agent selected from the group consisting of an androstane, an androstene, an estrane, an estrene, a pregnane, a pregnene, pharmaceutically acceptable salts thereof and combinations thereof. Preferably, the at least one additional active agent is selected from the group consisting of delta 4,16-androstadien-3-one, 1,3,5(10),16-estratetraen-3-ol, pharmaceutically acceptable salts thereof and combinations thereof. Preferably, the amount of delta 4,16-androstadien-3-one and/or 1,3,5(10),16-estratetraen-3-ol per dosage unit ranges between about 0.1 nmoles and about 100 nmoles, more preferably between about 0.5 nmoles and about 20 nmoles.

In an embodiment of the present invention wherein the at least one active agent is a form of nicotine or is a form of nicotine in combination with

at least one additional active agent, the composition is useful in at least one of smoking cessation therapy, nicotine replacement therapy or the treatment of smoking withdrawal syndrome.

In an embodiment of the present invention, the at least one active agent is a form of caffeine selected from the group consisting of caffeine, pharmaceutically-acceptable salts thereof and combinations thereof.

In an embodiment of the present invention, the at least one active agent is a form of ephedrine selected from the group consisting of ephedrine, pharmaceutically acceptable salts thereof and combinations thereof.

In an embodiment of the present invention wherein the at least one active agent is a form of caffeine and/or ephedrine, the composition is useful in improving at least one of performance or learning.

In an embodiment of the present invention, the at least one active agent is a form of testosterone selected from the group consisting of testosterone, pharmaceutically acceptable salts thereof and combinations thereof. Preferably, the at least one pharmaceutically acceptable carrier is lecithin organogel. Preferably, the form of testosterone is present in the composition in an amount ranging between about 0.001% and about 10.0% (w/w), more preferably ranging between about 0.1% and about 5.0% (w/w). When the composition is in unit dosage form, the amount of the form of testosterone per dosage unit ranges between about 0.05 mg and about 5 mg.

In an embodiment of the present invention wherein the at least one active agent is a form of testosterone, the composition is useful for increasing libido in a mammal.

In an embodiment of the present invention wherein the at least one active agent is a form of testosterone, the composition is useful for providing contraception to a male mammal.

In an embodiment of the present invention, the at least one active agent is 17ß-estradiol. Preferably, the at least one pharmaceutically acceptable carrier is a lecithin organogel. Preferably, the 17ß-estradiol is present in the composition in an amount ranging between about 0.000001% and about 0.01% (w/w), more preferably ranging between about 0.00001% and about 0.0005%

(w/w). When the composition is in dosage unit form, the amount of 17ß-estradiol per dosage unit ranges between about 0.05 µg and about 1.0 µg.

In an embodiment of the present invention, wherein the at least one active agent is 17ß-estradiol, the composition is useful to treat, prevent or reduce the severity of at least one perimenopausal symptom selected from the group consisting of hot flashes, short term memory loss, fuzzy thinking and combinations thereof.

In an embodiment of the present invention, wherein the at least one active ingredient is an estrogen, the composition is useful for providing contraception to a female mammal.

In an embodiment of the present invention, the at least one active agent is progesterone.

In an embodiment of the present invention, wherein the at least one active ingredient is a progestogen, the composition is useful for providing contraception to a female mammal.

In an embodiment of the present invention, wherein the at least one active agent is an estrogen in combination with a progestogen, the composition is useful for providing contraception to a female mammal.

In an embodiment of the present invention, the at least one active agent is selected from the group consisting of an androstane, an androstene, an estrane, an estrene, a pregnane, a pregnene, pharmaceutically acceptable salts thereof and combinations thereof. Preferably, the at least one active agent is selected from the group consisting of delta 4,16-androstadien-3-one, 1,3,5(10),16-estratetraen-3-ol, pharmaceutically acceptable salts thereof and combinations thereof. Preferably, the at least one pharmaceutically-acceptable carrier is a lecithin organogel. Preferably, the composition is in dosage unit form wherein the amount of delta 4,16-androstadien-3-one and/or 1,3,5(10),16-estratetraen-3-ol, per dosage unit ranges between about 0.1 nmoles and about 100 nmoles, more preferably between about 0.5 nmoles and about 20 nmoles.

In an embodiment of the present invention wherein the at least one active agent is an androstane or androstene, preferably delta 4,16-androstadien-3-one and/or an estrane or estrene, preferably 1,3,5(10),16-estratetraen-3-ol , the

composition is useful to elicit feelings selected from the group consisting of elation, euphoria, stimulation, friendliness, vigor, non-sexual alertness, relaxation, mellowness and combinations thereof.

In an embodiment of the present invention wherein the at least one active agent is an androstane or androstene, preferably delta 4,16-androstadien-3-one and/or 1,3,5(10),16-estratetraen-3-ol, the composition is useful to elicit the emotional and/or behavioral response of alerting in combination with relaxation or other similar thoughts, behaviors, moods and/or emotions in a female mammal.

In an embodiment of the present invention wherein the at least one active agent is an androstane or androstene, preferably delta 4,16-androstadien-3-one and/or an estrane or estrene, preferably 1,3,5(10),16-estratetraen-3-ol, the composition is useful prior to stressful situations as a confidence–builder and/or following stressful situations as an unwinder.

In an embodiment of the present invention wherein the at least one active agent is an androstane or androstene, preferably delta 4,16-androstadien-3-one and/or an estrane or estrene, preferably 1,3,5(10),16-estratetraen-3-ol, the composition is useful in the treatment of at least one disease or condition selected from the group consisting of obsessive-compulsive disorder, acute anxiety states and combinations thereof.

In an embodiment of the present invention wherein the at least one active agent is an androstane or androstene, preferably delta 4,16-androstadien-3-one and/or an estrane or estrene, preferably 1,3,5(10),16-estratetraen-3-ol, the composition may further comprise at least one additional active agent selected from the group consisting of a narcotic, an opiate, an opioid, an NMDA receptor antagonist and combinations thereof.

In an embodiment of the present invention wherein the at least one active agent is an androstane or androstene, preferably delta 4,16-androstadien-3-one and/or an estrane or estrene, preferably 1,3,5(10),16-estratetraen-3-ol, in combination with at least one additional active agent selected from the group consisting of a narcotic, an opiate, an opioid, an NMDA receptor antagonist and combinations thereof, the composition is useful to modulate pain states.

In an embodiment of the present invention wherein the at least one active agent is an androstane or androstene, preferably delta 4,16-androstadien-3-one and/or an estrane or estrene, preferably 1,3,5(10),16-estratetraen-3-ol, the composition may further comprise a form of caffeine selected from the group consisting of caffeine, pharmaceutically acceptable salts thereof and combinations thereof.

In an embodiment of the present invention wherein the at least one active agent is an androstane or androstene, preferably delta 4,16-androstadien-3-one and/or an estrane or estrene, preferably 1,3,5(10),16-estratetraen-3-ol, the composition may further comprise a form of ephedrine selected from the group consisting of ephedrine, pharmaceutically acceptable salts and combinations thereof.

In an embodiment of the present invention wherein the at least one active agent is an androstane or androstene, preferably delta 4,16-androstadien-3-one and/or an estrane or estrene, preferably 1,3,5(10),16-estratetraen-3-ol in combination with a form of caffeine and/or ephedrine, the composition is useful to improve at least one of performance or learning.

In an embodiment of the present invention wherein the at least one active agent is an androstane or androstene, preferably delta 4,16-androstadien-3-one and/or an estrane or estrene, preferably 1,3,5(10),16-estratetraen-3-ol, in combination with a form of caffeine, the composition is useful to counteract the irritability caused by the administration of caffeine alone.

In an embodiment of the present invention wherein the at least one active agent is an androstane or androstene, preferably delta 4,16-androstadien-3-one and/or an estrane or estrene, preferably 1,3,5(10),16-estratetraen-3-ol, the composition may further comprise at least one sex hormone selected from the group consisting of an androgen, an estrogen, a progestogen and combinations thereof. Preferably, the androgen is a form of testosterone selected from the group consisting of testosterone, pharmaceutically acceptable salts thereof and combinations thereof. Preferably, the estrogen is selected from the group consisting of estradiol, estriol, estrone, pharmaceutically acceptable salts thereof and combinations thereof. Preferably, the estradiol is 17ß-estradiol Preferably,

the progestogen is selected from the group consisting of progesterone, pharmaceutically-acceptable salts thereof and combinations thereof.

In an embodiment of the present invention wherein the at least one active agent is an androstane or androstene, preferably delta 4,16-androstadien-3-one and/or an estrane or estrene, preferably 1,3,5(10),16-estratetraen-3-ol, the composition may further comprise a form of testosterone selected from the group consisting of testosterone, pharmaceutically acceptable salts thereof and combinations thereof. Preferably, the at least one pharmaceutically-acceptable carrier is a lecithin organogel. Preferably, the form of testosterone is present in the composition in an amount ranging between about 0.001% and about 10.0% (w/w) and more preferably between about 0.1% and about 5.0% (w/w). When the composition is in unit dosage form, the amount of the form of testosterone per dosage unit ranges between about 0.05 mg and about 5 mg.

In an embodiment of the present invention wherein the at least one active agent is an androstane or androstene, preferably delta 4,16-androstadien-3-one and/or an estrane or estrene, preferably 1,3,5(10),16-estratetraen-3-ol, the composition may further comprise 17ß-estradiol. Preferably, the at least one pharmaceutically-acceptable carrier is a lecithin organogel. Preferably, the 17ß-estradiol is present in the composition in an amount ranging between about 0.000001% and about 0.01% (w/w) and more preferably between about 0.00001% and about 0.0005% (w/w). When the composition is in dosage unit form, the amount of 17ß-estradiol per dosage unit ranges between about 0.05 µg and about 1.0 µg.

In an embodiment of the present invention wherein the at least one active agent is an androstane or androstene, preferably delta 4,16-androstadien-3-one and/or an estrane or estrene, preferably 1,3,5(10),16-estratetraen-3-ol, the composition may further comprise progesterone.

In an embodiment of the present invention wherein the at least one active agent is an androstane or androstene, preferably delta 4,16-androstadien-3-one and/or an estrane or estrene, preferably 1,3,5(10),16-estratetraen-3-ol in combination with at least one sex hormone, the composition is useful in enhancing libido in a mammal.

In an embodiment of the present invention wherein the at least one active agent is an androstane or androstene, preferably delta 4,16-androstadien-3-one and/or an estrane or estrene, preferably 1,3,5(10),16-estratetraen-3-ol in combination with at least one sex hormone, the composition is useful to modulate the emotional effects caused by hormone fluctuations experienced by a mammal having at least one condition selected from the group consisting of pre-menstrual syndrome and menopause.

In an embodiment of the present invention wherein the at least one active agent is an androstane or androstene, preferably delta 4,16-androstadien-3-one and/or an estrane or estrene, preferably 1,3,5(10),16-estratetraen-3-ol, the composition may further comprise at least one of an anti-depressant, a tranquilizer and combinations thereof.

In an embodiment of the present invention wherein the at least one active agent is an androstane or androstene, preferably delta 4,16-androstadien-3-one and/or an estrane or estrene, preferably 1,3,5(10),16-estratetraen-3-ol in combination with least one of an anti-depressant, a tranquilizer and combinations thereof, the composition is useful to decrease the effective dosage amount of the anti-depressant and/or tranquilizer that is required to be administered to a mammal to obtain a desired effect.

In any one of the above embodiments of the present invention incorporating delta 4,16-androstadien-3-one, the recipient mammal is female.

In any of the above embodiments of the present invention, the composition or combination is useful to decrease the effective dosage amount of the at least one active agent that is required to be administered to a mammal to obtain a desired effect.

In any of the above embodiments of the present invention, the composition or combination is useful as an alternative and/or adjunctive route of administration to other major routes of administration which include, but are not limited to, enteral (oral) administration, sublingual administration, rectal administration, parenteral administration such as intravenous, subcutaneous, intramuscular, intraarterial and intrathecal, intraperitoneal injection, administration by inhalation (pulmonary absorption), topical application to the skin, eye and mucous membranes of the

conjunctiva, nasopharynx, oropharynx, vagina, colon, urethra, urinary bladder and the like including the nasal mucosa for the purpose of intravascular absorption of the active substance and/or for the purpose of chemosensory stimulation of receptor organs and/or nerve endings within the nose.

In any of the above embodiments of the present invention, the composition or combination is useful to reduce the risk to a mammal of contracting at least one needle-transmitted communicable disease and/or condition. Examples of needle-transmitted communicable diseases and/or conditions include, but are not limited to, hepatitis and acquired immunodeficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV).

In any of the above embodiments of the present invention, the at least one area of the nasal epithelium is selected from the group consisting of the vomeronasal epithelium, the respiratory epithelium, the lateral nasal epithelium and combinations thereof. The term "vomeronasal epithelium" as used herein includes at least one of the nasal epithelium overlying the vomeronasal organ, the nasal epithelium overlying the vomeronasal-terminalis neural pathway, the nasal epithelium proximate thereto and combinations thereof.

In any of the above embodiments, the composition or combination is applied or administered to the nasal mucosa of at least one of the pair of nasal cavities of the mammal. In one instance, the composition is applied or administered to the nasal mucosa with an applicator means. The applicator means may include, but is not limited to, a cotton swab, gauze, plastic spatula or the like. The composition or combination may also be applied or administered to the nasal mucosa using an individual's finger. The volume of the composition applied to the nasal mucosa of a nostril ranges from about 0.1 mL to about 0.3 mL.

In any of the above embodiments of the present invention, the at least one group of nerve fibers is selected from the group consisting of the vomeronasal-terminalis nerve fibers, the trigeminal nerve fibers, the autonomic nerve fibers and combinations thereof. The term "nerve fibers" as

used herein includes at least one of the axonal nerve fibers, the dendritic nerve fibers and combinations thereof.

In any of the above embodiments of the present invention, the at least one neural pathway is selected from the group consisting of the vomeronasal-terminalis neural pathway, the trigeminal neural pathway, the autonomic neural pathway and combinations thereof.

In any of the above embodiments of the present invention, the at least one active agent is transported to the brain via transneuronal transport. The term "transneuronal" as used herein means along nerve pathways. Transneuronal transport may be anterograde and/or retrograde and includes transport along axonal and/or dendritic nerve fibres and encompasses the movement of the active agents along the nerve surface and/or inside the nerve bundle and/or within individual nerve fibres and/or outside of, along or within nerve sheaths, that is, encompassing either or both of the intracellular and extracellular nerve environments. Transport of the active agents along the outside of the nerve can proceed either directly into the brain or into the CSF where the nerve crosses the subarachnoid space. The active agents are believed to enter the CSF directly if the perineural epithelium surrounding the axon is loosely adherent to the axon ("open-cuff" model), or through the epithelial cell junction if the perineural epithelium is closely adherent to the axon ("closed-cuff" model). The active agents are then believed to diffuse into the brain parenchyma from the CSF (See Illum, L., "Transport of drugs from the nasal cavity to the central nervous system", European Journal of Pharmaceutical Sciences, 11, (2000) 1-18). Therefore, in the present invention, transneuronal transport can occur within or along the vomeronasal-terminalis, trigeminal, and/or autonomic nerves directly into the brain, or along these nerves directly into the CSF and thence into the brain. The Applicant believes that the primary route of delivery of the active agents in the present invention is along or within the vomeronasal-terminalis, trigeminal and/or autonomic nerves directly into the brain.

In any of the above embodiments of the present invention, the at least one active agent is delivered to at least one brain center. The term "at least one brain center" as used herein means at least one anatomic and/or functional

type of brain cell. The at least one brain center includes, but is not limited to, the amygdala, the hypothalamus, the cingulate gyrus, the pre-frontal cortex, the temporal cortex, the pineal gland, the thalamus, and the limbic system. In one instance, the at least one brain center is within the diencephalon area.

In any of the above embodiments of the present invention, the at least one brain center is selected from the group consisting of a sexual brain center, a non-sexual brain center and combinations thereof.

In an embodiment of the present invention, the at least one brain center is involved in neuroendocrine regulation.

In an embodiment of the present invention, the at least one brain center is involved in the initiation and/or modulation of at least one of physiology, thought, emotion, mood, behavior and combinations thereof. The term "behavior" as used herein includes at least one of simple behavior, patterned complex behavior and combinations thereof. Preferably, the simple behavior is selected from the group consisting of anxiety, fear, aggression, rage, fight or flight response and combinations thereof. Preferably, the patterned complex behavior is selected from the group consisting of alerting and/or energizing a physical and/or intellectual state, sexual arousal, sexual attraction, addiction, sociability, happiness, euphoria, elation, increased intellectual and/or emotional receptiveness, relaxation, mellowing, and combinations thereof.

Other and further advantages and features of the present invention will be further understood from the following detailed description thereof.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

There is firm experimental evidence to support transneuronal transport into the brain of a variety of substances. The most comprehensive review of the literature is found in Mathison, S., Nagilla, R., Nasal route for direct delivery of solutes to the central nervous system. Journal of Drug Targeting, 5(6): 415-441 (1998). This article and those that are cited below underline that the research has focused on the intranasal entry point, absorption through olfactory epithelium and transport along olfactory nerves to the olfactory bulb in the brain.

Gopinath, P.G. was one of the first to elucidate this direct pathway to the brain. See Gopinath, P.G., Gopinath, G., Target site of intranasally sprayed

substances and their transport across the nasal mucosa: a new insight into the intranasal route of drug delivery. Curr. Ther. Res., 23: 596 (1978).

Seiler, M. found that nerve growth factor binds to receptors in axon terminals and can be internalized and retrogradely transported to the cell body of neurons. See Seiler, M., Brain Research, 300: 33-39 (1984).

Balin, B.J. found that radiolabelled progesterone appeared directly in the brain following intranasal administration. Balin, B.J., Broadwell, R.D., Avenues for entry of peripherally administered protein to the central nervous system in mouse, rat and squirrel monkey. J. Comp. Neurol., 251: 260 (1986).

Other types of molecules which were transported directly along the olfactory nerves were elucidated in the following publications:

Fabian et al, Intraneuronal IgG in the central nervous system: uptake by retrograde axonal transport. Neurology, 37: 1780-1784 (1987).

Pietrowsky, R., Brain potential changes after intranasal vs. intravenous administration of vasopressin: evidence for a direct nose-brain pathway for peptide effects in humans. Biological Psychiatry, 39(5): 332- 340 (1996).

Hussain, A.A., Intranasal Drug Delivery. Advanced Drug Delivery Reviews, 29(1-2):39-49 (1998).

Smolnik, R., Molle, M., Brain potentials and attention after acute and subchronic intranasal administration of ACTH 4-10 in humans. Neuroendocrinology, 70(1): 63-72 (1999).

Chow, H.S., Chen, Z., Direct transport of cocaine from the nasal cavity to the brain following intranasal cocaine administration in rats. J. Pharmaceutical Sciences, 88(8) 754-758 (1999).

Kern, W., Born, J., Central nervous system effects of intranasally administered insulin during euglycemia in man. Diabetes, 48(3): 557-563 (1999).

Sakane,T., Yamashita, S., Transnasal delivery of 5-fluoracil to the brain in the rat. Journal of Drug Targeting, 7(3): 233-240 (1999).

Henriksson, J., Transport of manganese via the olfactory pathway in rats: dosage dependency of the uptake and subcellular distribution of the metal in the olfactory epithelium and the brain. Toxicology and Applied Pharmacology, 156(2): 119-128 (1999).

Henriksson, J., Manganese uptake into the CNS via the olfactory pathway in rats affects astrocytes. Toxicological Sciences, 55(2): 392-398 (2000).

Larsson, P., Intranasal instillation of Aflatoxin B(0) in rats: Bioactivation of the nasal mucosa and neuronal transport to the olfactory bulb. Toxicological Sciences, 55(2): 383-391 (2000).

All of the research and development and prior art related to transneuronal transport from the nose to the brain has been focused on the olfactory epithelium and the olfactory neural pathway. There are at least two other types of nasal epithelium and associated neural pathways to the brain in addition to the olfactory: the epithelium overlying the vomeronasal organ (VNO) and its vomeronasal- terminalis nerve fibres and the respiratory and lateral nasal epithelium and their trigeminal nerve fibres. There are also autonomic nerve fibres. These pathways have not been the subject of research or prior art teachings in the area of direct brain transport of substances.

There is an embryologic basis for, and a pertinent example of, transneuronal transport along the vomeronasal system. Early in the embryologic life of mammals, there is migration of gonadotropin-releasing hormone immune reactive cells from the vomeronasal organ, along axons of the vomeronasal-terminalis nerve fibres, to the pre-optic hypothalamus. That is, during mammalian development, actual cells migrate along vomeronasal-terminalis nerves that run from the nose to the brain. See Pearson, A.A. The development of the nervus terminalis in man. J. Comp. Neurol. 75: 36066 (1941); Schwanzel-Fukuda, M., Pfaff, D., Structure and function of the nervus terminalis, In Handbook of Olfaction and Gustation, Doty, L. Ed. 38: 835-864 (1995).

The vomeronasal-terminalis nerve system warrants specific attention. It is unique and different from the olfactory system in a number of ways.

a) The vomeronasal epithelium and vomeronasal-terminalis nerve system, which opens onto the base of the nasal septum, is much more accessible to nasally-instilled or inhaled substances than is the olfactory epithelium, which is high up in the nose. The olfactory epithelium is too inaccessible to be reached by creams, gels or ointments, and requires liquids or

powders to be deposited in spray or aerosol form, whereas the vomeronasal epithelium is available to any type of carrier.

b) The vomeronasal-terminalis nerve system has a separate route and more extensive innervations to the brain than does the olfactory nerve. There are direct axonal connections from the human vomeronasal- terminalis nerve system to the amygdala and the hypothalamus. (In lower mammals, there is also a connection to the accessory olfactory bulb, but this structure is absent in humans). See Monti-Bloch, L., Jennings-White, C., Berliner, D.L., The human vomeronasal system. A review. Annals of the New York Academy of Sciences, 855: 373-389 (1998). This article also presents an excellent anatomic description of the vomeronasal organ and the vomernasal-terminalis nerve.

c) Not only are there distinct anatomic differences between the olfactory and the vomeronasal routes to the brain, there are also functional differences. The olfactory and vomeronasal nerves and their respective receptor organs are stimulated by different types of substances. The VNO, the receptor organ for the vomeronasal nerve, is stimulated by pheromone molecules, whereas the olfactory epithelium receptors are stimulated by odor molecules. Brain structures activated by pheromone-chemosensory stimulation of the VNO are different from those activated by odor-chemosensory stimulation of the olfactory epithelium. The former (demonstrated by functional brain imaging studies) comprise the hypothalamus, amygdala, cingulate gyrus, anterior thalamus, pre-frontal cortex and temporal cortex. See Prabhakaran, V., Comparison of brain activation following stimulation with odors and vomeropherins. Chem. Senses, 22: 771 (1997); Sobel, N., Prabhakaran, V., Blind smell: brain activation induced by an undetected air-borne chemical. Brain, 122: 209-217 (1999).

d) There are both physiologic and behavioral differences between olfactory chemosensory and vomeronasal chemosensory stimulation. The latter's effects are much more widespread. It induces specific, measurable and demonstrable changes in the autonomic system, hormonal systems (particularly in the hypothalamic-pituitary-gonadal axis) and in simple behavior. See Diaz-Sanchez, V., Monti-Bloch, L., Hypothalamic-pituitary-gonadal axis inhibition in normal men induced by delivery of pregna-4,20-

dien-3,6–dione to the vomeronasal organ. Chem. Senses 22: 670 (1997); Monti-Bloch, L., Grosser, B.I., Behavioral effect of androsta-4,16-dien-3-one (delta 4,16-androstadien-3-one). Chem. Senses 23:114 (1998); Monti-Bloch et al, Modulation of serum testosterone and autonomic function through stimulation of the male human vomeronasal organ (VNO) with pregna-4,20-diene-3,6-dione. J. Steroid Biochem. Molec. Biol., 65(1-6): 237-242 (1998).

e) There are both physiologic and behavioral differences between olfactory chemosensory and vomeronasal-terminalis transneuronal stimulation. The latter's effects are much more widespread. It induces specific, measurable and demonstrable changes in the autonomic system, hormonal systems (particularly in the hypothalamic-pituitary-gonadal axis) and in both simple and complex behaviors.

f) Most exciting in terms of the potential for targetted direct delivery, vomeronasal nerve stimulation can affect both sexual and non-sexual areas of the brain, whereas olfactory nerve stimulation appears to be limited to the latter. Electrical stimulation of the vomeronasal-terminalis nerve system can induce non-sexual brain changes such as reduction in anxiety (See Jennings-White, C. et al, United States Patent No. 6,057,439: Steroids as neurochemical stimulators of the VNO to alleviate symptoms of PMS and anxiety; Grosser, B.I., Behavioral and electrophysiological effects of delta 4,16-androstadien-3-one, a human pheromone. Psychoneuroendocrinology, 25(3) 289-299 (2000); Chen, D., Haviland-Jones, J., Rapid mood change and human odors. Physiology and Behavior, 68(1-2) 241-250 (1999); Pause, B.M., Rogalski, K.P., Sensitivity to androstenone in female subjects is associated with an altered brain response to male body odor. Physiology and Behavior, 68(1-2): 129-137 (1999); Jacob, S. and McClintock, M.K., Psychological State and Mood Effects of Steroidal Chemosignals in Women and Men. Hormones and Behaviour, 37:57 - 78 (2000)).

Sexual stimulation as well as hormonal modulation by the nasal route has been documented by Cutler, W. et al, since the early 1980's, but it has only been in the last decade that her findings have been linked to the vomeronasal rather than the olfactory system. See Cutler, W.B., Preti, G., Human axillary secretions influence women's menstrual cycles: the role of donor extract from

men. Horm. Behav., 20: 463-473 (1986); Preti, G. et al, Human axillary secretions influence women's menstrual cycles: The role of donor extract from women. Horm. Behav., 20: 474-482 (1986); Preti, G., Cutler, W.B., Human axillary extracts: analysis of compounds from samples which influence menstrual timing. J. Chem. Ecol. 13: 717-731 (1987); Cutler, W.B., Friedmann, E., Pheromonal influences on sociosexual behavior in men. Archives of Sexual Behavior, 27(1): 1-13 (1998); Cutler, W.B. United States Patent No. 5155045: Use of male essence to alter female endocrine response.

Sexual stimulation has been documented indirectly by Rauch S. and by Stoleru S. by demonstrating that the sexual centers activated by VNO stimulation are coincident with those activated during sexual arousal by visual and other means. See Rauch, S., Neural activation during sexual arousal in healthy men. Psychiatry Research, 91(1): 1-10 (1999); Stoleru, S., Neuroanatomical correlates of visually evoked sexual arousal in human males. Archives of Sexual Behavior, 28(1): 1-4 (1999).

In summary, the vomeronasal-terminalis route to the brain offers a more fertile ground for direct substance delivery than does the olfactory route.

All of the research and development and prior art related to the vomeronasal system focus on chemosensory stimulation of the vomeronasal organ, with consequent electrical stimulation of the vomeronasal nerve and resultant electrical stimulation of brain. Not only has the direct transport of pheromones, vomeropherins and other substances along the vomeronasal-terminalis nerve system into the brain with resultant brain stimulation been generally ignored, it has been specifically discounted by, for example, Monti-Bloch et al. Monti-Bloch teaches the following: "These results suggest that chemosensory information processed in the VNO reaches the brain through a polysynaptic neural path. Therefore, an effect of vomeropherins through mucosal absorption and direct action on central structures is unlikely." See p. 383 Monti-Bloch et al, The human vomeronasal system. A Review. Supra. Thus, the results of Monti-Bloch teach away from the present invention such that a person skilled in the art, reading Monti-Bloch et al., is led in a direction divergent from the path Applicant took in the present invention.

The present invention provides a method of transneuronal transport of substances from inside of the nose to the brain via nerve pathways, particularly the vomeronasal-terminalis nerve pathway and a composition to effect such transport.

The neural pathway from the nose to the brain and particularly the vomeronasal-terminalis neural pathway provide a direct route from the exterior of the body to the brain which circumvents the systemic circulation and thus the blood-brain and blood-CSF barriers altogether. Substances are transported along anterograde and/or retrograde neural pathways connecting the nose and the brain. This is a very different delivery mechanism from that resulting from the traditional instillation of substances into the nose, whereby they either are absorbed into the bloodstream and travel to different parts of the body, or they chemically stimulate nerve receptors in the nasal mucosa, with resultant electrical stimulation of nerves leading to the brain. The areas of the brain targeted by transneuronal transport are also quite different from those reached by transportation across the blood-brain and/or blood-CSF barriers from the circulation.

The neural pathways from the nose to the brain and particularly the vomeronasal-terminalis neural pathway, can be visualized as a transneuronal 'escalator' or 'conveyor belt' from the nose to the brain. The characteristics of the present invention that make transneuronal transport from the nose to the brain possible and unique include, but are not limited to, the following:

1) the nerve pathway from the nose to the brain is one of the shortest in the body;

2) the nerve pathway is uninterrupted by synapses; there is only one axon connecting the nose and the brain;

3) the nerve pathway is unmyelinated in contrast to most nerves in the body;

4) the at least one pharmaceutically-acceptable carrier or vehicle of the present invention for use in combination with at least one active agent, has the unique ability to a) traverse the nasal mucosa and b) facilitate movement of the at least one active agent along nerve pathways into the brain.

Transneuronal transport from the nose to the brain, particularly along the vomeronasal-terminalis nerves, delivers substances directly and specifically to the diencephalon area (thalamus, hypothalamus, pineal gland, limbic system) as opposed to the global delivery (cerebral cortex, cerebellum, etc.) of blood-brain barrier transport. The ability to target and influence the areas of the brain that are involved in neuroendocrine regulation (hypothalamus, pineal gland) and in initiation of emotions and patterned complex behavior (thalamus, limbic system) has profound consequences in the medical and behavioral sciences.

Strong evidence in support of the transneuronal transport of substances according to the present invention as opposed to or in addition to intravascular absorption/blood-brain barrier transport of substances is disclosed in Examples 2 and 10 below.

The present invention is directed to, but is not limited to, the following:

1) Delivering, for diagnostic or therapeutic purposes, one or more natural and/or synthetic substances from the nasal mucosa directly to the brain, by means of transneuronal transport primarily along the vomeronasal-terminalis nerve system which links the nose and the brain, and in some cases along one or more subsidiary transneuronal pathways, namely, trigeminal and/or autonomic nerves. Vomeronasal- terminalis transneuronal transport provides a) a new method of entry for substances which cannot traverse the blood-brain barrier, or b) an enhanced method of entry for substances which can traverse the blood-brain barrier.

2) Initiating or modulating thoughts, behavior or emotions, by stimulating one or more of the sexual and/or non sexual centers of the brain directly, as a result of delivery of substances into the brain. Stimulation of one or more of the sexual and/or non sexual centers of the brain indirectly, (by means of chemosensory stimulation of the vomeronasal organ, with consequent stimulation of the vomeronasal nerve and resultant electrical stimulation of the brain) may occur concomitantly, but is neither a necessary nor a sufficient condition for the efficacy of this invention.

Diagnostic and therapeutic purposes and applications are anticipated, and include, but are not limited to the prevention or treatment of disease or

dysfunction states; the modification of the natural aging process; the modification of the mammalian genome or of any of the biological (intracellular or extracellular) activities which result therefrom; modulation of mammalian sexual physiology and/or behavior, thoughts, moods, emotions; modulation of mammalian non-sexual physiology and/or behavior, thoughts, moods, emotions; and stimulation of the brain.

Stimulation of the brain results in the initiation and/or modulation of moods, emotions, behavior and/or thoughts. The mammalian brain is stimulated by the input of energy. This is accomplished by the following modalities:

a) transfer of electrical, electro-magnetic, mechanical or thermal energy through the skull;

b) the intravascular delivery of substances to and across the blood-brain and/or blood-CSF barriers (See United States Patent No. 5,179,079 supra);

c) the instillation of substances directly into the brain or cerebrospinal fluid;

d) the transneuronal anterograde and retrograde transport of chemical molecules along neural pathways connecting the nasal mucosa and the brain (See United States Patent No. 5,624,898 supra);

e) chemical, physicosensory, or chemosensory stimulation of receptor organs for sight, hearing, taste, smell and touch (including heat, vibration and pain) with consequent electrical stimulation of the innervating neuron;

f) the chemosensory stimulation of a putative sexual arousal receptor organ, the vomeronasal organ; with consequent electrical stimulation of the vomeronasal nerve (the mechanism for which is addressed by Monti-Bloch, L., The Human Vomeronasal Organ. Psychoneuroendocrinology, 196: 73-86 (1994); and by Berliner D.L., United States Patent Nos. 5,272,134 and 5,278,141); and

g) the thought process itself, whereby electrical and/or chemical energy is transferred from one area of the brain to another.

The quality of brain stimulation can be sexual, non-sexual or both.

Sexual arousal is one of the most complex forms of behavior because of the number of permutations of brain stimulation (potentially any or all of modalities (a) to (g)). Current research has focused on modality (f), stimulation of the VNO by pheromones. A pheromone is a biochemical produced by one individual, which when inhaled, elicits a specific physiologic or behavioral response in another individual of the same species. The hypothesis of one group of researchers (Berliner, Monti-Bloch, Jennings-White, supra) is reductionistic: a substance of one molecular structure, when applied to the vomeronasal organ, will trigger one specific behavioral response. What has been demonstrated by them (cumulative publications, supra) is i) that different chemical molecules applied to the VNO produce different clusters of brain stimulation effects (in terms of brain electrical activity, brain hormone release and resultant autonomic nervous system activity); ii) these effects can be different in males and females; iii) there may be resultant non-complex behavioral effects, such as decrease in anxiety. The chemical structures of these molecules have all been steroidal: estrogen-, androgen- and progesterone-related in structure. In summary, Berliner et al have demonstrated that certain synthetic steroidal molecules, when applied to the VNO of members of the opposite sex, act as pheromones, but no single molecule or limited mixture thereof has resulted in complex behavioral changes. (See United States Patent Nos. 5,792,757, 5,922,699, 5,939,570, 5,965,552, 6,057,439, 6,066,627). Even though numerous areas of the brain are activated by single chemicals (See Sobel N., Blind Smell, supra), the physiologic or behavioral responses demonstrated by the application of single chemicals are extremely narrow in scope. Changes in skin temperature, galvanic skin response, alpha-cortical activity and even in blood levels of LH and testosterone are a far cry from modulation of complex human behavior such as sexual arousal.

The research of Cutler, WL., on the other hand, takes a more holistic approach to brain stimulation and the modulation of human behavior. See United States Patent Nos. 4,670,401 and 5,155,045 supra. Cutler teaches i) that neuroendocrine modification to the female menstrual cycle can be effected by the exposure to male axillary secretions; ii) that certain human male pheromones may affect the sexual attractiveness of men to women. See Cutler,

W.L., Pheromonal Influences on Sociosexual Behavior in Men, supra). Cutler's cumulative research, combined with that of McClintock, M.K., Menstrual synchrony and suppression. Nature, 229: 244-245 (1971) and Stern, K., McClintock, M.K., Regulation of Ovulation by Human Pheromones. Nature, 392 (6672): 126-127, 177-179 (1998), points to the alternate hypothesis: the more complex the behavior one wishes to initiate or modulate, the more complex i) the mix of pheromones applied to the VNO must be and/or ii) the greater the varieties of brain stimulation (a) to (g) supra, must be.

The premise that there must be a complex mix of pheromones, rather than just one or two, to initiate or modulate complex behavior, is bolstered by the work of Tirindelli, R. Tirindelli has shown that there are many different chemosensory receptors of two distinct classes in the VNO, not just one or two. See Tirindelli, R., Molecular aspects of pheromonal communication via the vomeronasal organ of mammals. Trends in Neurosciences, 21 (11): 482-486 (1998). The most compelling evidence is provided by Jacob, S., and McClintock, M.K., supra. Jacob and McClintock show that two of the steroid molecules referred to in United States Patent No. 5,278,141(delta 4,16-androstadien-3-one and 1,3,5,(10),16-estratetraen-3-ol) do not initiate complex behavior in men or women. Rather, they appear to modulate discrete elements of mood, such as elation, irritation, anxiety, anger, and they do so differently in the two sexes. The conclusions of Jacob and McClintock are: "Human behaviors and psychological states are multifaceted and are determined by the interplay of a wide variety of stimuli. Therefore, it is unlikely that delta 4,16-androstadien-3-one or any other potential communicative chemical signal, is sufficient for triggering stereotyped behavior.... These compounds would be unique among human sensory stimuli if they could trigger complex behavior in a fixed-action pattern....Although sexual effects are generally implied by marketing claims with perfumes containing these steroids, our reported general effects on mood suggest that simple, stereotyped releaser effects on sexual behavior would be unlikely.... It may be critical that pheromones are not isolated but associated with carrier proteins or a cocktail of other chemicals and scents".

The composition of pheromones is also in disagreement. They are not limited to steroid molecules, as proposed by Berliner et al. Tirindelli's

discovery of many different chemosensory receptors of two distinct classes in the VNO leads to the conclusion that there appears to be a role for some proteins and small molecules, as well as steroids, as pheromones. Ryba demonstrates that the issue of receptor complexity in the VNO is paralleled in the brain: the map of pheromone activation is far more complex than that of olfactory activation. See Ryba, N.J., Pheromone reception: A complex map of activation in the brain. Current Biology, 9(13): R472-474) (1999). Finally, pheromones are produced by apocrine and/or eccrine and/or sebaceous glands and secreted onto the skin surface of mammals. Pheromones comprise both volatile and non-volatile compounds. Bernier has found 346 compound peaks of volatile chemicals alone! See Bernier, U.R., Kline, D.C., Analysis of human skin emanations by gas chromatography/mass spectrometry. Analytical Chemistry, 72(4): 747-756 (2000). Preti has analyzed chemical composition from human axillary secretions, one of the more fertile sources of pheromones and has similarly found a multiplicity of compounds. See Preti, G., Human axillary extracts: analysis of compounds from samples which influence menstrual timing. J. Chem. Ecol. 13: 717-731 (1987).

In short, knowledge about the influence of pheromones on brain stimulation which results in behavioral changes, is rudimentary. However, observation of mammalian behavior provides a strong indicator that there is "chemistry" between individuals of the same species. Sexual arousal is related to inhaling skin emanations from another. One approach to initiating or modifying a complex behavior (that taken by Berliner et al) is to isolate and synthesize individual molecules from the hundreds and potentially thousands of components of skin secretions, apply them individually and in an almost infinite number of mixtures to the VNO, until the desired behavior pattern is achieved. This is an Herculian task, not only in terms of the number of combinations and permutations of mixtures, but also because we know nothing about potential synergies among compounds, how compounds are modified by nasal mucosal secretions, or whether components of skin secretions, if not themselves pheromones, have an ancillary function, such as potentiators or inhibitors of chemosensory stimulation of the VNO. As indicated earlier, it is doubtful that patterned complex behavior can be initiated

or modified by individual molecules, in any event. An alternative approach adopts the teachings of Cutler, and utilizes natural secretions, rather than synthesized molecules, to stimulate the brain. Regardless of the approach, every research effort and invention cited above has relied on a simple liquid carrier such as saline, ethanol, or propylene glycol, which required pheromone/vomeropherin molecules to be either sprayed onto or into the nasal mucosa, or inhaled. The goal was only to stimulate the vomeronasal organ. Because the issue of transneuronal transport was overlooked, no effort was made to utilize specific carriers which could transfer pheromones directly into the brain. Therefore, all pheromone teachings and inventions are solely based on VNO chemosensory stimulation, and as such, are incomplete and possibly inaccurate.

The thrust of Applicant's research builds on the Cutler, rather than the Berliner hypothesis: to consistently achieve brain stimulation resulting in complex behavior initiation or modulation, specifically sexual arousal, it is more efficacious to emulate and amplify rather than to parse and dissect Nature. There are four aspects to amplification of a natural effect: the nature of the stimulatory substance applied to the receptor, the concentration of the stimulatory substance applied to the receptor, the type of modality employed to stimulate the brain [selected from modalities (a) to (g) supra] and the number of modalities employed concurrently.

Applicant has consequently investigated methods of collecting and delivering pheromones in a way which parallels and amplifies nature. In nature, the inhalation of skin secretions is pleasurable. It can certainly be sexually arousing, but it is also anxiolytic and comforting. The sniffing-upon-greeting behavior of most mammals is a graphic representation not only of the prevalence of pheromone inhalation activity, but also of the preferred site of production. The richest mixture of potential pheromones and pheromone potentiators is found in the skin secretions of the perineum and the inner thighs of post-pubertal males and females. It is secreted constantly onto the skin surface, but is produced most copiously during sexual activity. Collection of these secretions, and application in an appropriate transneuronal carrier

material to the nasal mucosa of post-pubertal individual, has consistently produced brain stimulation of a pleasurable nature in the recipient.

Whereas the generic nature of direct brain stimulation by skin secretions, produced by the present invention, is 'alerting', it may also be sexually arousing, anxiolytic, or energizing in a non-sexual competitive or creative vein. The specific behavioral responses will vary from individual to individual, depending on the immediately pre-stimulatory brain state and on the social situation: work, play, romance, etc.

The nature and intensity of response in recipient B may depend not only on B's unique brain characteristics, but also on the origin of the stimulatory substances. Donor A's complement of secretions are not identical to donor C's. In fact, the composition of each individual's skin secretions may be as unique as his/her fingerprints. This may be the basis for the presence or absence of 'sexual chemistry' between individuals or classes of individuals. In addition, the composition of skin secretion may vary with other physiological parameters, such as hormone balance. For instance, it is known that the composition of vaginal secretions, which contain pheromones, fluctuates along with the menstrual cycle

Applicant has made the following discoveries:

1) The collection, concentration and application to the nasal mucosa of individual B of the total complement of individual A's skin secretions, utilizing the specific transmucosal carrier/vehicle of this invention, is significantly more efficacious for brain stimulation than sniffing A's skin directly.

2) The transfer of all or part of the total complement of A's skin secretions to the brain of B by the transneuronal vomeronasal-terminalis route, utilizing the specific transmucosal carrier/vehicle of this invention, is significantly more efficacious than chemosensory stimulation of B's VNO by these substances (and consequent electrical stimulation of the vomeronasal-terminalis nerve and thereby electrical stimulation of the brain). Instillation of all or part of the total complement of A's skin secretions onto nasal mucosa overlying B's VNO, utilizing the specific transmucosal carrier/vehicle of this invention, and resulting in i) transneuronal vomeronasal-terminalis transfer,

ii) electrical vomeronasal stimulation, possibly iii) intravascular absorption with transfer across the blood-brain barrier, and probably iv) thoughts of the erotic nature of the action and its anticipated results, is significantly more efficacious than chemosensory stimulation of B's VNO alone (the result of sniffing or inhaling pheromones).

3) The application of the total complement of an individual's skin secretions to the nasal mucosa of another has a number of differences from the natural or experimentally-designed sniffing of those secretions. The differences are as follows:

i) One can sniff only volatile molecules. There are many non-volatile components to collected skin secretions.

ii) The concentration of molecules which actually reach the nasal mucosa in sniffed secretions is a fraction (possibly 1/1000) of that of collected secretions which are applied directly to the nasal mucosa. Even when the recipient of sniffed secretions is in intimate contact with the donor, the resultant nasal concentrations of inhaled molecules is estimated to be in picograms per millilitre. See United States Patent No. 5,278,141.

iii) Pheromones in sniffed secretions stimulate the brain by modality (f) only. Pheromones in collected secretions, in the carrier/vehicle of the present invention, can stimulate the brain by modalities (d) alone, or modalities (f) and (d) and possibly modality (b), thereby further amplifying the central effect.

Thus, the sniffing of volatile pheromones from the skin of another has a fraction of the effect of collecting the total complement of skin secretions, depositing it on the nasal mucosa overlying the vomeronasal- terminalis nerves. The latter achieves direct brain stimulation via the transneuronal transport mechanism as well as chemosensory stimulation of the VNO. The novelty of the findings is that chemosensory stimulation of the VNO is not required in order to achieve the desired physiologic or behavioral effect; vomeronasal- terminalis transneuronal transport is the necessary and sufficient operative mechanism (see Example 10).

These discoveries have influenced the Applicant to develop novel methods of pheromone transfer so that i) equivalent or enhanced brain

stimulation can be achieved without intimate contact; ii) enhanced brain stimulation can be achieved during intimate contact.

The type of carrier/vehicle and the physico-chemical properties of the carrier/vehicle are critical for the successful operation of the transneuronal transport mechanism. Applicant has investigated a variety of carrier agents, which have the potential to transfer both hydrophilic and lipophilic substances across the nasal mucosa in a non-toxic, non-irritating manner. Applicant has made the following discoveries:

1) Some substances that are absorbed through the nasal mucosa, and are absorbed therefrom into the bloodstream but are not normally able to cross the blood-brain barrier, are able to reach the brain via the transneuronal vomeronasal-terminalis route.

2) Some substances that are absorbed through the nasal mucosa, and are absorbed therefrom into the bloodstream and are normally able to cross the blood-brain barrier, are able to also reach the brain via the transneuronal vomeronasal-terminalis route.

3) Transneuronal delivery of substances from the nose to the brain is achievable because the connecting (vomeronasal and terminalis) nerves are unmyelinated, and therefore may be more accessible to penetration and transport of substances along or within the nerve by the specific carrier/vehicle formulations of this invention.

These discoveries have influenced the inventor to develop novel methods of substance transfer so that i) substances which cannot normally cross the blood-brain barrier will have a new, safe route of entry into the brain; ii) substances which can cross the blood-brain barrier can be delivered in much lower doses than required by oral, topical or injection routes.

Transneuronal transport along the vomeronasal-terminalis system, with potential adjunctive transport along trigeminal and/or autonomic nerve pathways, is an alternative and very different route to the intravascular, blood-brain barrier route. Stimulation of sexual or other brain centers by a number of modalities concurrently (one or more traditional modalities plus transneuronal transport) may be not only more efficacious, but also different in effect than stimulation by one or more traditional modalities.

The present invention provides for a method for delivering natural and/or synthetic substances to the nasal mucosa, and from there to the brain. Elements of the invention include, but are not limited to, the following:

1) A) Delivering substances to the brain directly, by means of transneuronal transport along the vomeronasal-terminalis nerves, and potentially the trigeminal and/or autonomic nerves. This involves: i) preparing substance/vehicle mixtures; ii) instilling mixtures on the nasal mucosa overlying the vomeronasal nerve, thereby resulting in delivery of substances to the brain by the transneuronal anterograde and/or retrograde transport along neural pathways connecting the nasal mucosa and brain. This is aforementioned modality (d);

B) Delivering substances to the brain indirectly, by means of the intravascular route across the blood brain barrier. This involves i) preparing substance/vehicle mixtures; ii) instilling mixtures on the nasal mucosa, thereby resulting in the absorption of the substances into the bloodstream and delivery to the brain, and entry into the brain by transiting the blood-brain barrier. This is aforementioned modality (b). This is not a necessary condition for efficacy of the invention, but may the unavoidable consequence of depositing certain mixtures onto the nasal mucosa.

2) Collection and delivery of a mixture of substances from the skin surface of donor mammal A that has the effect of stimulating the brain and particularly one or more of the sexual centers of the brain of another mammal of the same species. This involves: i) collection of moisture consisting of apocrine, eccrine and sebaceous gland secretions derived from perineum, thighs and/or axillae (and possibly vagina or urethra) of a mammal, with a solvent that has both lipophilic and hydrophilic characteristics; ii) the admixture of this solution with a carrier or vehicle which has both hydrophilic and lipophilic properties and/or characteristics; permucosal and/or transmucosal penetration characteristics; non-toxicity and non-irritability to the mucosa and nerve tissue; ability to insinuate solute in or around nerve tissue; iii) the application of the substance/carrier to the inside of the nose, to the mucosa overlying the chemoreceptor(s) and/or nerve pathway desired of recipient mammal B.

The carrier or vehicle characteristics described for 2) above equally apply to 1)A) and B) above.

The carrier or vehicle can be in the form of, but is not limited to, one or a combination of the following: oil- water emulsion, microemulsion, organogel, lecithin organogel, lecithin microemulsion, vesicle, micelle, proliposome, liposome, soluble synthetic polymer, block co-polymer micelle, microsphere, microsponge.

3) the mixing of one or more substances with that obtained by method (2) above, for the purpose of stimulating the brain and particularly one or more of the sexual centers of the brain of the donor mammal or another mammal of the same species;

4) A) Stimulating one or more of the sexual and/or non sexual centers of the brain directly, by means of 1 (A) and/or 1 (B) above. This is aforementioned modality (d), or modalities (d), (b) and/or (c).

B) Stimulating one or more of the sexual and/or non sexual centers of the brain indirectly, by means of chemosensory stimulation of the vomeronasal organ, with consequent stimulation of the vomeronasal nerve and resultant electrical stimulation of the brain. This is modality (f).

Stimulating one or more of the sexual and/or non sexual centers of the brain directly or indirectly may also include one or more of modalities (a), (e), (g).

The present invention permits substances of many compositions and uses, including therapeutic and diagnostic agents, vaccines, hormones, intracellular modifiers and pheromones to be delivered directly to the brain, either bypassing or supplementing the blood-brain barrier and direct injection routes, by means transneuronal transport. The preferred route of transport is via the vomeronasal-terminalis nerve system; however, it may also comprise one or more of the trigeminal and/or autonomic nerve systems. This invention also discloses brain stimulation methods.

The present invention discloses a method for delivering substances to mammalian nasal mucosa, and thence either directly or directly and indirectly to the brain. The method involves the suspension or dissolution of one or more substances in an appropriate carrier or vehicle and instilling the

resultant mixture in specified quantities onto designated areas of the nasal mucosa. The carrier or vehicle has both hydrophilic and lipophilic properties and/or characteristics; permucosal and/or transmucosal penetration characteristics; non-toxicity and non-irritability to the mucosa and nerve tissue; ability to insinuate solute in or around nerve tissue. The carrier or vehicle can be in the form of, but is not limited to, one or a combination of the following: oil-water emulsion, microemulsion, organogel, lecithin organogel, lecithin microemulsion, vesicle, micelle, proliposome, liposome, soluble synthetic polymer, block co-polymer micelle, microsphere, microsponge.

The novel aspects of the delivery system embodied in the present invention include, but are not limited to, the following:

i) that substances, particularly drugs that are unable to penetrate the blood-brain barrier [modality (b)] and that previously would require injection into the brain or CNS [modality (c)], now have a alternate, more convenient and safer route of delivery [modality (d)];

ii) substances, particularly drugs that can penetrate the blood-brain barrier now have an additional and/or preferred route of entry. As a result, lower dosages of drugs may be required to achieve the equivalent diagnostic or therapeutic physiologic or behavioral effect, or an enhanced effect may be effected with a dose comparable to the oral, transdermal, transmucosal, or injected dose.

Examples of neuro-active drugs which are embraced by the present invention include, but are not limited to, members of classes of the following: nicotine base, its salts and major metabolites and analogues; caffeine and its salts; narcotics and narcotic antagonists, including opioids, opiates; NMDA receptor antagonists; anxiolytic agents; antidepressant agents; analgesics; anti-migraine agents; anti-convulsant agents; anti-obsessional agents; anti-psychotic agents; anti-Parkinsonian agents; anti-mania agents; agents for the treatment of eating disorders, Alzheimer's Disease, attention deficit and other learning disorders, memory disorders, cognitive disorders; sex hormones, their analogs, precursors and metabolites; hypothalamic and pituitary hormones and releasing factors; agents affecting the autonomic nervous system; appetite-suppressant agents; libido-modulating agents; mood-modulating agents;

vitamins; minerals; bacteria, viruses and other organisms; DNA, RNA and substances that modify the mammalian genome or its resultant biological effects.

Examples of novel uses of the present invention include, but are not limited to, the following:

i) Pharmaceuticals that cannot cross the blood-brain barrier: Some antibiotics required for the treatment of encephalitis require intrathecal (into the cerebro-spinal fluid) injection. Intranasal administration will be a welcome alternative or adjunct.

ii) Pharmaceuticals that can cross the blood-brain barrier but require other than oral administration (because of alteration in the GI tract or by the liver): testosterone base cannot be ingested orally. Other forms of administration are inconvenient or painful. Intranasal administration will be a welcome alternative or adjunct.

iii) Pharmaceuticals that can cross the blood-brain barrier, but need to be directed exclusively or primarily to the brain, with no or minimal distribution to other organs of the body: Women or men may require the delivery to the brain of one or more sex hormones such as testosterone or estrogen, in the absence of delivery to peripheral target sex organs. For instance, a peri-menopausal female may suffer from decreased libido, and require testosterone intracerebrally, but not wish to experience the masculinizing side effects to skin and voice that intravascular delivery entails. A peri-menopausal female may suffer from the cognitive deficits that estrogen depletion causes, and require estrogen intracerebrally, but not wish to risk the increased risk of breast cancer that intravascular delivery entails. Similarly, an andropausal male may suffer from decreased libido and require testosterone intracerebrally, but will not accept the increased risk of activating a pre-existing prostate carcinoma that intravascular testosterone entails. Another use for intranasal testosterone and intranasal estrogen or estrogen/progesterone as conceived in this invention is as male or female contraceptive, respectively, as a result of suppression of FSH and LH secretion.

iv) Pharmaceuticals that can cross the blood-brain barrier: Decreased dosage of a narcotic, anxiolytic, anti- depressant or other class of medication can

be effected by the direct or direct plus indirect route to the brain, in comparison to the indirect (intravascular route). If a drug is ingested orally, it can be partially or completely metabolized by the liver before reaching the brain, and it is usually taken up by other organs before reaching the brain. Approximately 1/5 to 1/10 of the drug dose should be required if the drug is administered and completely absorbed intranasally, because a) if transferred through the nasal mucosa into the bloodstream, the route to the brain is the shortest of any intravascular route (only a few inches) and b) if transferred through the nasal mucosa along one or more of the nerve systems, there is no diluting effect by blood or uptake by other organs. An example of this is the investigation of Mattsson, L.A., of intranasal spray 17 beta-estradiol (S21400), which is absorbed into the bloodstream through the nasal mucosa. Conclusion: "Intranasal administration of 300 micrograms per day estradiol was at least as effective as oral administration of 2 milligrams per day estradiol in alleviating postmenopausal symptoms, with less frequent mastalgia and uterine bleeding and without the metabolic consequences of the first-pass effect". Mattson, L.A., Clinical equivalence of intranasal and oral 17 beta-estradiol for postmenopausal symptoms. American J. Obs. Gyn., 182(3): 545-552 (2000).

Although intranasal drug delivery has been a topic of research and development for many years, it is only within the past decade that carrier systems have been devised which make delivery of substances, and particularly of large molecules, feasible. See Sayani, A., Chien, Y.W., Systemic delivery of peptides and proteins across absorptive mucosae. Critical Reviews in Therapeutic Drug Carrier Systems, 13 (1 & 2): 85-184 (1996). However, the focus has been entirely (with the exception of US Patent No. 5624898 supra) on intranasal instillation of substances for absorption into the bloodstream as opposed to direct transport into the brain. Examples of the former are found in United States Patent No. 5,179,079 and 4,383,993. Thus, carriers/vehicles have been developed, primarily in the form of sprays and liquid drops, with the purpose of penetrating the nasal mucosa and introducing their solutes into the bloodstream. This usually entails the addition of penetration enhancers into an aqueous solution, primarily because of an inverse relationship between size of the solute molecule and its penetrability through nasal mucosa and blood

vessel wall. Carriers/vehicles which facilitate transneuronal transport have significantly different requirements and characteristics. They must not only be able to penetrate the nasal mucosa, but also to insinuate solute molecules around or within the nerve fascicle or fibre, and facilitate movement of those molecules into the brain. Very few carriers can meet these criteria and also be non-irritating and non-toxic to the nasal mucosa.

Examples of preferred embodiments of the at least one pharmaceutically-acceptable carrier or vehicle of the present invention and its uses include, but are not limited to, the following:

The at least one pharmaceutically-acceptable carrier or vehicle has the following characteristics. It can be a liquid, cream, gel or ointment. It does not irritate the nasal mucosa or underlying nerves, or provide a health risk. It has minimal odor. It may be an accepted transcutaneous or percutaneous carrier or vehicle, because any carrier that can effectively penetrate the stratum corneum of the skin should be highly efficacious in not only penetrating mucosa, but also allowing rapid absorption of substances into the vasculature, submucosal organs, nerve sheaths and nerves. Particularly in cases where the nerves are unmyelinated, a carrier with a chemical structure similar to that of nerve components is most likely to facilitate the transfer of substances along nerves. Prime examples of such compounds include, but are not limited to phosphatidylcholine, phosphatidylserine, sphingomyelins.

A lecithin or phosphatidylcholine organogel cream is one preferred pharmaceutically-acceptable carrier or vehicle of the present invention, which will be used as the reference model for all of the following examples.

Lecithin has become recognized as a possible permeation enhancer in the transdermal delivery of drugs. Studies have also revealed that, by adding small amounts of water to solutions of lecithin (for example molar rations of water to lecithin of about 3 and about 12, respectively) in organic solvents (for example cyclohexane or ethanol), produce generic formulations called lecithin organogels. Lecithin organogels make vehicles of suitable viscosity for topical application and are currently used for transdermal drug delivery (see Dreher, F., Walde, P., Interaction of a lecithin microemulsion gel with human stratum corneum and its effect on transdermal transport. J. Contr. Release, 45: 131-140

(1996); Willimann, H., Luisi, P.L., Lecithin organogels as matrix for the transdermal transport of drugs. Biochem. Biophys. Res. Comm., 177(3): 897-900 (1991); Willimann, H., Walde, P., Lecithin organogel as matrix for transdermal transport of drugs. J. Pharm. Sciences, 81(9): 871-874 (1992)).

Lecithin organogels are made of two different phases – a water phase and an oil phase. The water phase is the part of the gel which provides a carrier for water-soluble active agents and makes the gel more cosmetically pleasing. The lecithin phase is the oil phase of the gel and is composed of lecithin micelles and/or liposomes and/or proliposomes, which form a matrix within the gel that absorbs or encapsulates the active agent for delivery across the epithelium. This is where most active agents reside. The micellar and/or liposomal composition of lecithin organogels provides enhanced penetration or transportation of the active agent through the epidermis and effective delivery of the active agent to the target area. One theory is that in making a careful mixture of lecithin and polymer, a gel is made that closely mimics the cellular cement that holds cells together. In this way, the active agent gets around the cells and into the target area, instead of making the active agent travel through the cells. This provides a much quicker penetration and provides an excellent way to get active agents into the target area. Another theory is that the lecithin organogel slightly disorganizes the structure of the cells, and thus, permits the permeation of various active agents. It is the Applicant's additional theory that the physico-chemical properties of the lecithin organogel not only permit the insinuation of active substances around certain nerves, but also facilitate their transfer along nerve pathways.

One such example of a preparation used to prepare the at least one pharmaceutically-acceptable carrier of the present invention contains phosphatidylcholine derived from soya bean lecithin, isopropyl palmitate, a polymer stabilizer, a preservative and anti-bacterial agent, and less than 5% ethanol. The aqueous/oil ratio is between about 3/1 and about 4/1.

Another such example of a lecithin organogel base used as the at least one pharmaceutically-acceptable carrier of the present invention is PHLOJEL® Ultra as supplied by J.A.R. Pharmaceuticals Ltd., Edmonton, AB, Canada. PHLOJEL® Ultra is a topical lecithin organogel base consisting of lipids and a

polymer, formulated in a vehicle of water and alcohol to yield a gel. The base is compatible with a wide variety of active agents, which may be either dissolved or suspended. PHLOJEL® Ultra offers a broad matrix for the accommodation of greater percentages of active agents. For example, a finished product of up to at least about 20% of the at least one active agent is attainable.

The above information regarding PHLOJEL® Ultra was obtained from the internet homepage of J.A.R. Pharmaceuticals Ltd. (http://www.phlojel.com) and a webpage of one of their suppliers, Xenex Laboratories Inc. (http://xenex.hcsn.com/transdermal.ihtml).

Applicant has discovered that lecithin organogels have ideal characteristics for nasal transmucosal delivery of many active agents, and do not seem to require enhancers to penetrate the nasal mucosa, as do most other transmucosal carriers. Applicant has also discovered that the unique penetrating power of lecithin organogels makes it an ideal carrier for the at least one active agent to transport/deliver the at least one active agent across/through the nasal epithelium to at least one group of nerve fibres where it can be delivered to the brain by means of at least one neural pathway.

Further details of the preferred embodiments of the present invention are illustrated in the following examples which are understood to be non-limiting. The following examples were carried out as limited clinical trials supervised by a licensed medical doctor. Compositions in these examples were prepared by the simple trituration of active ingredient(s) with carrier/vehicle.

EXAMPLE 1

The dissolution of nicotine base or one of its salts in a lecithin organogel cream of the composition described above, in concentrations ranging from 0.01% to 2%. The Applicant has named this substance EROSNUFF™. One 'dab' of EROSNUFF™ to each nostril would deliver a dose of nicotine not exceeding 2 mg. The amount of nicotine ingested with one puff of a cigarette is generally less than 1.5 mg. There are 3 uses for EROSNUFF™: nicotine replacement in a weaning situation in smoking-cessation therapy; nicotine replacement by committed smokers in smoke-free environments; nicotine replacement in nicotine- addicted individuals who wish to give up tobacco but not nicotine. For chronic nicotine users, EROSNUFF™ may actually reduce the amount of

nicotine required for the equivalent degree of brain stimulation, because of the multi-input stimulation which intranasal input initiates [any or all of modalities (b), (d), (e), (f)]. The same model applies for caffeine and other addictive drugs such as narcotics.

Subject 1 applied 0.25 mg of nicotine base (in an EROSNUFF™ formulation) to each nostril whenever she had the urge to smoke (approximately once every 2 hours while awake). Each application satisfied the urge within seconds. She remarked that intranasal EROSNUFF™ provided the same nicotine "buzz" as did cigarettes, which was absent with nicotine patches, nicotine gum and EROSNUFF™ applied to the oral buccal mucosa. [Patches and gum may provide the same absolute amount of nicotine to the brain, but over a much longer period of time than does EROSNUFF™, thereby eliminating withdrawal side effects but not providing the concentrated jolt of nicotine that the addict requires]. She felt that she could use EROSNUFF™ to wean herself off of nicotine, but preferred to use it as an alternate form of nicotine ingestion. The buccal mucosa is a preferred site for the transmucosal/intravascular absorption of substances. The lack of nicotine "buzz" with buccal transmucosal application (intravascular delivery) as compared to nasal transmucosal application (intravascular and transneuronal delivery), is evidence that the "buzz" is due to transneuronal delivery.

Subject 1 compared 0.5 mg nicotine in carrier (Example 1) with 0.5 mg nicotine plus 10 nanomoles delta 4,16-androstadien-3-one in carrier. She felt calmer and less agitated with the latter mixture and definitely preferred it. She commented that it was a "happier fix".

Subject 2 was a committed smoker, who had significant difficulty abstaining in smoke-free environments such as hospitals, public buildings and airplanes. He used intranasal EROSNUFF™ (0.25 mg nicotine in each nostril) in those situations as a cigarette substitute. In contrast, EROSNUFF™ applied to the oral buccal mucosa did not satisfy his craving for nicotine. This is additional evidence in support of the transneuronal delivery of nicotine by means of this invention.

Subject 3 was a non-smoker and non-nicotine user, who applied 1 mg. nicotine intranasally twice, 12 hours apart, on day. On day 2, he experienced

severe nicotine withdrawal symptoms: irritability, restlessness, craving. This is a profound effect, and certainly would not be expected after the equivalent dose of nicotine obtained by 1-2 puffs of a cigarette on 2 separate occasions. It indicates significant binding of nicotine molecules to receptors in the brain, when nicotine is delivered by the vomeronasal transneuronal route.

EXAMPLE 2

The dissolution of testosterone base or one of its salts in a lecithin organogel cream of the composition described above, in concentrations ranging from 0.01% to 6%.

Subject 4 was receiving testosterone injections (100 mg. intramuscularly once a week) as a contraceptive. (Exogenous testosterone in appropriate doses will suppress the pituitary release of FSH and LH, thereby stopping both sperm and testosterone production in the testes). He discontinued the injections until he experienced significant decrease in libido, as well as elevated FSH and LH blood levels. He thereupon commenced 1/30 of the previous I.M. dose per day of intranasal testosterone (1.75 mg. twice daily) in the aforementioned carrier. He experienced an increase in libido within 24 hours and his blood levels of FSH and LH were again suppressed and remained so throughout the course of administration. There was no statistically significant elevation in free testosterone blood levels 30 minutes after instilling intranasal testosterone, indicating that the mode of action is transneuronal transport rather than transmucosal absorption/blood-brain barrier transport.

In summary, with oral, intravenous, intramuscular, buccal transmucosal, transdermal or subcutaneous pellet administration of large doses of testosterone, hypothalamic-pituitary FSH and LH secretion is suppressed and blood levels of these two hormones drop, while the free testosterone blood level rises. This is the predictable action of the gonadal-hyopthalamic-pituitary negative feedback system. When the brain receives testosterone from an outside source, it "tells" the testes to stop making its own, but the blood level of free testosterone increases as a result of repeated exogenous administration. With intranasal administration of testosterone in the carrier of the present invention, on the other hand, blood levels of FSH and LH drop, but free testosterone blood level also drops. This is because the

hypothalamus is receiving testosterone transneuronally rather than in the bloodstream and across the blood-brain barrier. The hypothalamus again "tells" the testes to stop making testosterone, which it does, but now, there is either no testosterone or insufficient testosterone entering the bloodstream from the intranasal application to raise blood levels of this hormone. Subject 4 then refrigerated his supply of testosterone in carrier. This effectively modified the physico-chemical structure of the carrier, inducing coalescence and increased size of liposomes and micelles. The purpose was to render ineffective the transneuronal transport characteristics of the carrier, while preserving the transmucosal transport characteristics. In this way, testosterone would still be transported across the nasal mucous membrane, but instead of being preferentially transported along nerve tracts into the brain, it would be primarily or exclusively absorbed into the bloodstream and be transported across the blood-brain barrier. Accordingly, his FSH and LH blood levels remained low, and his free testosterone blood level rose significantly and continued to rise with repeated twice daily intranasal application. This parallels the effect of oral, IM., IV., transdermal or buccal transmucosal transport, because the testosterone is now being transported from the nose directly into the bloodstream rather than into the nerve tracts. This demonstrates definitively: 1) that there are two distinct immediate pathways for substances when applied intranasally: a) into the bloodstream, b) along nerve tracts; 2) that there are 2 distinct pathways for substances to enter the brain: a) across the blood-brain barrier, b) along the vomeronasal-terminalis nerve system; 3) that the physico-chemical properties of the carrier are critical for the success of intranasal transneuronal transport of substances as opposed to intranasal intravascular absorption of substances. All intranasal transmucosal inventions (with the exception of the aforementioned United States Patent No. 5,624,898 to Frey and the present application), rely on absorption of substances into the bloodstream through the nasal mucosa as opposed to absorption through the nasal mucosa into, around and along nerve tracts.

Subject 5 was the partner of subject 4. She wished to increase her libido above normal. She applied 1.75 mg. testosterone intranasally. She noticed an

increase of libido within a few minutes of application. This effect was consistent over the course of 2 weeks. There was no statistically significant elevation in free testosterone blood levels 30 minutes after instilling intranasal testosterone, indicating that the mode of action is transneuronal transport rather than transmucosal absorption/blood-brain barrier transport.

EXAMPLE 3

Subject 6 was experiencing the following perimenopausal symptoms: hot flashes, short-term memory loss, fuzzy thinking. She applied 0.1 micrograms of 17 beta-estradiol intranasally per day. She noted a decrease in frequency of hot flashes, an improvement in short-term memory and disappearance of fuzzy thinking. Symptoms returned when she ceased use of the estrogen product.

In summary, transneuronal transport allows substances which cannot reach the brain through the traditional route of blood-brain barrier transport to do so. For substances which can cross the blood-brain barrier, it is anticipated that pharmaceuticals of many of the aforementioned classes will be able to be administered in lower doses to achieve the equivalent physiologic or behavioral effect, with the intranasal administration of this invention, or will be able to target the brain and avoid or minimize uptake by other organs. The mixture of different classes of neurochemicals (eg. addition of mood modulators such as delta 4,16-androstadien-3-one) may achieve specific advantageous effects, such as more rapid analgesia, or more efficacious withdrawal from addictive substances. The direct delivery of substances to the thalamus, hypothalamus, limbic system with this invention, may have specific diagnostic, therapeutic or behavioral effects which cannot be otherwise achieved. Although this invention relies on transneuronal vomeronasal-terminalis and/or trigeminal, autonomic nerve transport and specifically excludes transport along the olfactory nerve, it nevertheless encompasses processes whereby substances are delivered to both pathways and achieve diagnostic, therapeutic or behavioral effects which would not be obtained by olfactory nerve transport alone.

The present invention also contemplates the use of the above-mentioned compositions and methods in other mammals besides humans.

For example, male feed pigs are physically castrated at birth to increase the meat yield. This, however, creates boar-taint. The meat has a different taste which is noticeable to some people. The present invention offers two potential solutions: 1) the daily application of intranasal testosterone, with results similar to that of Example 2 above, and 2) the delivery of a radioactive or other ablating or modifying gonadotropin releasing-factor agent, (with the carrier of the present invention) to the hypothalamus, in order to achieve chemical and hypothalamic, as opposed to physical and gonadal castration.

The present invention also provides a method for the collection of the total complement of mammalian skin secretions and their delivery to the nasal mucosa of another individual in an appropriate carrier or vehicle. The skin secretions may or not be mixed with another substance which has a physiological or behavioral effect on the brain. The method for collection involves the dissolving of skin secretions of donor individual A in a solvent that has both hydrophilic and hydrophobic properties, transferring the resultant solution to the at least one pharmaceutically-acceptable carrier of the present invention, and after an appropriate period of time during which the carrier has extracted the skin secretions, applying the mixture to the nasal mucosa overlying the vomeronasal-terminalis nerve of recipient individual B. The properties and characteristics of the carrier or vehicle correspond to those described above.

The novel aspects of the method of brain center stimulation embodied in the present invention is that i) non-volatile as well as volatile components of skin secretions are delivered both to the vomeronasal organ and to the vomeronasal-terminalis nerve. In nature, the sniffing of skin secretions only delivers volatile components, and only delivers them to the VNO [modality (f)], but not to the nerve [modality (d)]. However, non-volatile components are equally important. They may act as additional separate pheromones, or as potentiators or enhancers of direct [modality (d)] or indirect [modality (f)] brain stimulation; ii) the concentration of volatile components is many-fold higher than by sniffing; iii) sniffing engages modality (f) and possibly modality (e). This invention engages modality (f), and one or more of modalities (b), (d), (e), (g); iv) the action of nasal mucosal enzymes on non-volatile components of

skin secretions and/or on the carrier, can create new pheromones or potentiators or enhancers of either pheromone action or pheromone mucosal penetration, which do not occur during the act of sniffing, or at all in nature.

Examples of novel uses of the present invention include, but are not limited to, the following:

i) Pheromones collected from donor individual A are transferred intranasally to recipient individual B, by applying the carrier cream/gel containing the skin secretions of the donor to the nasal mucosa of the recipient. The brain is stimulated by transneuronal transfer of pheromones along the vomeronasal- terminalis nerve system. Concomitantly, the VNO of the recipient is stimulated in a chemosensory manner, thereby stimulating the vomeronasal nerve and thereby the brain.

ii) Pheromones collected by individual A are mixed with one or more other substances, such as a sex hormone, or a mood enhancer, prior to instillation inside the nose of the recipient.

Examples of preferred embodiments of the present invention and their uses include, but are not limited to the following:

The at least one pharmaceutically acceptable carrier or vehicle used in the following embodiments, has the same characteristics as already mentioned.

Skin secretions are collected, preferably following intercourse or self-stimulation, from the (previously washed) perineum and the inside of the thighs of the donor individual. Secretions may also be collected from the axillae. Vaginal or penile secretions or ejaculates, which contain specific pheromones called copulins may also be collected. Collection is accomplished by wiping the skin sites with a gauze (preferably non-woven) or similarly absorbent swab, which has been pre-wetted with ethyl alcohol (40%-80%). The swab is then immersed in 3-5 gm. of aforementioned carrier gel, within a closed container. After a minimum of 12 hours of time, during which the secretions are extracted into the gel, a dab of the gel is applied to the nasal mucosa overlying each vomeronasal nerve of the recipient individual. This application can be repeated in 5-10 minutes. Brain stimulation, in the form of an alerting behavior, and possibly a sexual arousal behavior, will occur within a few minutes of application. This kit is called EROSEX™.

Example uses of this drug carrier system and method of delivery, carried out as limited clinical trials under the supervision of a licensed medical doctor, include:

EXAMPLE 4

Subject 7 applied EROSEX™ derived from a female subject A, to his nasal mucosa 2-5 times daily for week 1. He reported an immediate alerting sensation within a few minutes of each application, which persisted for 15-30 minutes. When in mixed company during that time period, he was more aware of the opposite sex and more sexually aroused. This was particularly noticed during business meetings, when he would not usually have sexual thoughts. When alone immediately following application, he felt paradoxically more relaxed as well as more alert. He could prolong the experience with a second application of EROSEX™ within 30 minutes of the first application. Subject 7 repeated the procedure during weeks 2 and 3 with skin secretions derived from female subjects B & C respectively. Responses were identical.

EXAMPLE 5

Female subjects A, B, and C applied skin secretions derived from subject 7, 2-5 times daily during weeks 1 and 2. They reported both an immediate alerting and a sexual arousal, which persisted for 20-30 minutes.

EXAMPLE 6

Subject A suffered from acute anxiety attacks with obsessional elements. She reported that she could reduce the severity of these attacks, and on 2 occasions within the 2 week EROSEX™ application period, actually abort the attacks, by the instillation of subject 7's skin secretions.

EXAMPLE 7

Subject 8 applied skin secretions derived from subject B to his nasal mucosa, during work as a hairdresser, with no prior knowledge of what the gel contained or its purpose. He became alert within a few minutes and was distracted from his work by the women in the room. He commented that sexual arousal in a work situation was totally out of character. The effect persisted for 15 to 20 minutes. Subject 8 is also a body- builder. He commented that he consistently experienced a more powerful workout after applying subject B's skin secretions to his nasal mucosa before exercising, indicating that

an alerting/energizing effect (without sexual arousal) is achieved when the invention is used in a non-sexual situation.

EXAMPLE 8

Subject 9 applied skin secretions derived from female subject D to his nasal mucosa and vice versa. They both became sexually aroused within a few minutes. Sexual arousal recurred with subsequent applications, whether applications occurred when the individuals were together or separate.

EXAMPLE 9

Female subject E applied skin secretions derived from subject 9 to her nasal mucosa, prior to going to sleep alone, for a period of 1 week. She was normally a very restless sleeper, waking frequently during the night when alone. She commented that she could only sleep well when her nose was snuggled into subject 9's armpit. She noted a similar uninterrupted sleep when sleeping alone, after applying subject 9's skin secretions.

EXAMPLE 10

Female subject F was sexually aroused whenever she applied the skin secretions derived from male subject 10 to her nasal mucosa. Her nasal mucosa was anesthetized with 2% Lidocaine. She then applied subject 10's skin secretions in the carrier. She became sexually aroused. This indicates that transneuronal transport of pheromones [modality (d)] is operative in stimulation of sexual brain centers, with this invention, as opposed to chemosensory stimulation of the VNO [modality (f)]. On a separate occasion, she applied subject 10's skin secretions in the carrier to her buccal mucosa. She noted no sexual arousal or other behavioral, emotional and/or physiological effects. This indicates that transneuronal transport of pheromones [modality (d)] is operative in stimulation of sexual brain centers in this invention, as opposed to intravascular absorption and transport across the blood-brain barrier [modality (b)].

On a separate occasion, she applied 10 nanomoles of delta 4,16-androstadien-3-one to her nasal mucosa in the same carrier used for skin secretions, after her nasal mucosa was anesthetized with 2% Lidocaine. She noted an increase in non-sexual mood, specifically, euphoria, elation, friendliness, vigor within a few minutes of application. This indicates that

transneuronal transport of pheromones [modality (d)] is operative in stimulation of non-sexual brain centers in this invention, as opposed to chemosensory stimulation of the VNO [modality (f)]. On yet another occasion she applied 10 nanomoles of delta 4,16-androstadien-3-one to her buccal mucosa (inside her mouth) in the same carrier used for skin secretions. The buccal mucosa is a preferred site for the transmucosal/intravascular absorption of substances. She noted no emotional or behavioral effect. This indicates that transneuronal transport of pheromones [modality (d)] is operative in stimulation of non-sexual brain centers in this invention, as opposed to intravascular absorption and transport across the blood-brain barrier [modality (b)]. Lidocaine is an amide local anaesthetic which prevents the generation and conduction of the nerve impulse. (See Catterall, W., The Pharmacological Basis of Therapeutics, Ninth Edition, McGraw-Hill: 331 (1996)). It not only numbs the inside of the nose, it also prevents the electrical stimulation of the vomeronasal nerve by the vomeronasal organ. Sexual response to pheromones after application of Lidocaine to the nasal mucosa is strong evidence that transneuronal transport of pheromones is the operative mechanism of this invention, rather than electrical stimulation of the vomeronasal nerve as proposed by Monti-Bloch et al. Thus, although chemosensory stimulation of the vomeronasal organ [modality (f)] may also occur when skin secretions in one of the carriers of this invention are applied to the nasal mucosa, this is neither a necessary nor a sufficient condition for efficacy of this invention.

EXAMPLE 11

Female subject F applied 5 nanomoles of delta 4,16-androstadien-3-one in the same carrier used for EROSEX™, to each area of her nasal mucosa overlying the vomeronasal organ. Within 2 minutes she noted increases in feelings of elation, euphoria, stimulation, friendliness, vigor, alertness, as well as a relaxed feeling. She compared these moods with those achieved by the application of skin secretions (Example 10). She stated skin secretions produced both a more intense and a more sexually-oriented reaction, whereas delta 4,16-androstadien-3-one produced a non-sexual alerting and mellowness simultaneously. When delta 4,16-androstadien-3-one was mixed with skin

secretions in the carrier, she noted no difference in mood from that induced by skin secretions in the carrier alone. The results of Examples 2, 10 and 11 have been documented repeatedly and consistently, resulting in the conclusion that the operative mechanism for this invention is i) transneuronal transport rather than chemosensory stimulation or intravascular/blood-brain barrier transport, ii) vomeronasal-terminalis transneuronal transport rather than olfactory transneuronal transport.

In summary, all subjects applied EROSEX™ ad libidum to the nasal septum of the lower one third of the nose. This localized application to the area overlying the vomeronasal-terminalis nerve specifically excluded the area overlying the olfactory nerve (which is inaccessible by finger in any event). The application rate averaged 5 times in a 24 hour period. Most female subjects admitted to an increased rate of masturbation during the test period. They felt that not only were they more sexually aroused as a result of EROSEX™ application, and therefore more likely to self-stimulate, but also that the intranasal application actually enhanced the self-stimulatory experience. The male response was less one of sexual arousal than of generalized energizing and sexual alerting. Both sexes found the EROSEX™ experience highly pleasurable. Consistency of response, plus plasticity (ability to modulate behavior in either a sexual stimulatory or anxiolytic direction, as needed), gives EROSEX™ a unique function among neuro-active agents.

While all embodiments and examples describe collection of skin secretions from one individual and transfer to another, it is within the scope of this invention that collections from more than one individual be pooled in one carrier or vehicle. Similarly, collection sites can include any anatomical area which produces secretions. Finally, other substances, such as sex hormones or libido or sexual performance enhancers, or mood modulators such as delta 4,16-androstadien-3-one, or brain stimulants such as ephedrine or nicotine, can be added to the skin secretions prior to instillation in the nose. It is foreseen (but not condoned) that illicit drugs such as Ecstasy or cocaine may be mixed into the carrier in place of or in addition to skin secretions. The incorporation of illicit drugs into the at least one pharmaceutically-acceptable carrier of the present invention to obtain a composition and the application of

the composition to the nasal mucosa is an alternative route of administration to that of intravenous illicit drug use and has the beneficial effect of reducing the risk to a mammal of contracting at least one needle-transmitted communicable disease and/or condition. Examples of needle-transmitted diseases and/or conditions include, but are not limited to, hepatitis and acquired immunodeficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV).

Because the EROSEX™ invention was devised as a 'do it yourself' pheromone collection delivery system, multiple user variations on the collection and/or delivery protocols, as well as extemporaneous uses, are anticipated. Potential uses of EROSEX™ include but are not limited to the following:

1) when donor and recipient are of opposite sex and heterosexual:

(a) to elicit pleasurable moods, such as alerting, sexual arousal, relaxation, energizing, increased creativity;

(b) to enhance pleasurable sensations and responses during periods of intimacy.

2) when donor is male or female and recipient is female:

(a) modulation of menstrual cycle;

(b) modulation of PMS symptoms;

(c) modulation of perimenopausal, menopausal and postmenopausal symptoms.

3) when donor and recipient are of the same sex and homosexual:

a) to elicit pleasurable moods, such as alerting, sexual arousal, relaxation, energizing, increased creativity;

(b) to enhance pleasurable sensations and responses during periods of intimacy.

Another element of the present invention is the unique emotional and/or behavioral response of alerting in combination with relaxation obtained when females applied delta 4,16-androstadien-3-one in the carrier of this invention, to the nasal mucosa overlying the vomeronasal-terminalis nerve. This response pattern has not been obtained with any known pharmaceutical and is a surprising discovery, with many clinical applications.

It can be used prior to stressful situations, as a confidence-builder, and following stressful situations, as an 'unwinder'. It can be used as an alternative to alcoholic beverages. It is a treatment for obsessive-compulsive disorder and acute anxiety states and can be mixed into the carrier of this invention in combination with other substances, eg.

i) narcotics (opiates and opioids), and/or NMDA receptor antagonists, to modulate pain states,

ii) caffeine, to improve performance or learning and/or counteract the irritability caused by caffeine,

iii) nicotine, to enhance the smoking-withdrawal or smoking replacement experience,

iv) sex hormones, to enhance libido or modulate emotions effects of hormone fluctuation, as seen in PMS, andropause, menopause,

v) antidepressants or tranquillizers, to decrease dosage while maintaining effects.

Numerous modifications, adaptations and variations may be made to the embodiments of the invention described above without departing from the scope of the invention which is defined in the claims.

While the foregoing provides a detailed description of a preferred embodiment of the invention, it is to be understood that this description is illustrative only of the principles of the invention and not limitative. Furthermore, as many changes can be made to the invention without departing from the scope of the invention, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE AS FOLLOWS:

1. A composition for use in administering at least one active agent to the nasal mucosa of a mammal and delivering the at least one active agent through at least one area of nasal epithelium, to at least one group of nerve fibers, along at least one neural pathway and into the brain of the mammal, the composition comprising: at least one active agent in combination with at least one pharmaceutically-acceptable carrier with the proviso that the at least one area of nasal epithelium is not the olfactory epithelium, the at least one group of nerve fibers is not the olfactory nerve fibers and the at least one neural pathway is not the olfactory neural pathway.

2. The composition of Claim 1 wherein the at least one active agent is capable of at least one of delivering itself through the at least one area of the nasal epithelium, delivering itself to the at least one group of nerve fibers, delivering itself along the at least one neural pathway, delivering itself into the brain of the mammal and combinations thereof.

3. The composition of Claim 1 or 2 wherein the amount of the at least one active agent administered is substantially less than the amount of the at least one active agent which would normally be administered to the mammal to be delivered to the brain by the vascular route to achieve a substantially similar effect.

4. The composition according to any one of Claims 1 to 3 wherein the at least one active agent is selected from the group consisting of a therapeutic agent, a prophylactic agent, a diagnostic agent, an agent which stimulates the brain of a mammal, an agent which initiates and/or modulates at least one of the physiology, behavior, thoughts, moods or emotions of a mammal and combinations thereof.

5. The composition according to any one of Claims 1 to 4 wherein the at least one active agent is selected from the group consisting of at least one component of

at least one secretion collected from at least one skin surface of at least one donor mammal, cholinomimetic agents, central nervous system stimulants, sedatives, narcotics, narcotic antagonists, opioids, opiates, NMDA receptor antagonists, anxiolytic agents, anti-depressant agents, tranquilizers, analgesics, anti-migraine agents, anti-convulsant agents, anti-obsessional agents, anti-psychotic agents, anti-Parkinsonian agents, anti-mania agents, agents for the treatment of eating disorders, agents for the treatment of Alzheimer's Disease, agents for the treatment of attention deficit disorders, agents for the treatment of learning disorders, agents for the treatment of memory disorders, agents for the treatment of cognitive disorders, hormones, hormone releasing factors, pheromones, vomeropherins, agents which affect the autonomic nervous system, appetite-suppressant agents, libido-modulating agents, mood-modulating agents, vitamins, minerals, infective agents, agents which modify the mammalian genome or any of the biological effects (intracellular or extracellular) which result therefrom, vaccines, intracellular modifiers, contraceptive agents, anti-viral agents, anti-bacterial agents, anti-neoplastic agents, anti-parasitic agents, anti-inflammatory agents, anti-fungal agents, hypnotic agents, anti-emetic agents, tranquilizers, diagnostic agents, agents which modify the natural aging process of a mammal, agents for the diagnosis and/or treatment of chemical addictions, agents for the treatment of sleep disorders and combinations thereof.

6. The composition Claim 5 wherein the cholinomimetic agent is selected from the group consisting of nicotine base, pharmaceutically-acceptable salts thereof, metabolites thereof, analogs thereof and combinations thereof.

7. The composition Claim 5 wherein the central nervous system stimulant is selected from the group consisting of caffeine, ephedrine, pharmaceutically-acceptable salts thereof and combinations thereof.

8. The composition Claim 5 wherein the hormone is selected from the group consisting of a sex hormone, analogs thereof, precursors thereof, metabolites thereof and combinations thereof.

9. The composition Claim 8 wherein the sex hormone is selected from the group consisting of an androgen, an estrogen, a progestogen and combinations thereof.

10. The composition of Claim 9 wherein:

(a) the androgen is selected from the group consisting of testosterone, pharmaceutically-acceptable salts thereof and combinations thereof;

(b) the estrogen is selected from the group consisting of estradiol, estriol, estrone, pharmaceutically acceptable salts thereof and combinations thereof; and

(c) the progestogen is selected from the group consisting of progesterone, pharmaceutically-acceptable salts thereof and combinations thereof.

11. The composition of Claim 10 wherein the estradiol is 17ß-estradiol.

12. The composition of Claim 8 wherein the precursor of a sex hormone is selected from the group consisting of delta 4,16-androstadien-3-one, 1,3,5(10),16-estratetraen-3-ol, pharmaceutically acceptable salts thereof and combinations thereof.

13. The composition of Claim 5 wherein the hormone is selected from the group consisting of a pituitary hormone, a hypothalamic hormone and combinations thereof.

14. The composition of Claim 5 wherein the infective agent is selected from the group consisting of bacteria, viruses and combinations thereof.

15. The composition of Claim 5 wherein the hormone releasing factor is selected from the group consisting of a hypothalamic hormone releasing factor, a pituitary hormone releasing factor and combinations thereof.

16. The composition of Claim 5 wherein the agent which modifies the mammalian genome is selected from the group consisting of DNA, RNA and combinations thereof.

17. The composition of Claim 5 wherein the diagnostic agent is selected from the group consisting of a monoclonal antibody, a polyclonal antibody, a chemical reagent and combinations thereof.

18. The composition of Claim 17 wherein the diagnostic agent is labeled with a labeling agent selected from the group consisting of a radioactive agent, an enzymatic agent, a fluorescent agent and combinations thereof.

19. The composition of Claim 18 wherein the diagnostic agent is an antibody and is labeled by means of a reaction with a second labeled antibody.

20. The composition according to any one of Claims 1 to 19 wherein the at least one pharmaceutically-acceptable carrier facilitates the delivery of the at least one active agent through the at least one area of the nasal epithelium, to the at least one group of nerve fibers, along the at least one neural pathway, and to the at least one brain center of the mammal and combinations thereof.

21. The composition according to any one of Claims 1 to 20 wherein the at least one pharmaceutically-acceptable carrier is selected from the group consisting of an oil-water emulsion, a microemulsion, an organogel, phosphatidylcholine, phosphatidylserine, sphingomyelin, a phosphatidylcholine organogel, a lecithin organogel, a lecithin microemulsion, a vesicle, a micelle, a proliposome, a liposome, a soluble synthetic polymer, a block co-polymer micelle, a microsphere, a microsponge and combinations thereof.

22. The composition according to any one of Claims 1 to 21 wherein the composition is in a form selected from the group consisting of a liquid, a powder, a spray, an aerosol, drops, a cream, a gel, and an ointment.

23. The composition according to any one of Claims 1 to 22 wherein the at least one area of the nasal epithelium is selected from the group consisting of the vomeronasal epithelium, the respiratory epithelium, the lateral nasal epithelium and combinations thereof.

24. The composition according to any one of Claims 1 to 23 wherein the vomeronasal epithelium is selected from the group consisting of the nasal epithelium overlying the vomeronasal organ, the nasal epithelium overlying the vomeronasal-terminalis neural pathway, the nasal epithelium proximate thereto and combinations thereof.

25. The composition according to any one of Claims 1 to 24 wherein the at least one group of nerve fibers is selected from the group consisting of the vomeronasal-terminalis nerve fibers, the trigeminal nerve fibers, the autonomic nerve fibers and combinations thereof.

26. The composition according to any one of Claims 1 to 25 wherein the at least one neural pathway is selected from the group consisting of the vomeronasal-terminalis neural pathway, the trigeminal neural pathway, the autonomic neural pathway and combinations thereof.

27. The composition according to any one of Claims 1 to 26 wherein the at least one active agent is transported to the brain via transneuronal anterograde transport, transneuronal retrograde transport and combinations thereof.

28. The composition according to any one of Claims 1 to 27 wherein the at least one active agent is delivered to at least one brain center.

29. The composition of Claim 28 wherein the at least one brain center is selected from the group consisting of a sexual brain center, a non-sexual brain center and combinations thereof.

30. The composition of Claim 28 or 29 wherein the at least one brain center is within the diencephalon area.

31. The composition according to any one of Claims 29 to 31 wherein the at least one brain center is selected from the group consisting of the amygdala, the hypothalamus, the cingulate gyrus, the pineal gland, the thalamus, the limbic system, the prefrontal cortex, the temporal cortex and combinations thereof.

32. The composition according to any one of Claims 28 to 31 wherein the at least one brain center is involved in at least one of neuroendocrine regulation, modulation of physiology, initiation and/or modulation of thoughts, initiation and/or modulation of emotions, initiation and/or modulation of moods or initiation and/or modulation of behavior.

33. The composition according to any one of Claims 1 to 32 wherein the at least one active agent is a form of nicotine selected from the group consisting of nicotine base, pharmaceutically-acceptable salts thereof, metabolites thereof, analogs thereof and combinations thereof.

34. The composition of Claim 33 wherein the at least one pharmaceutically-acceptable carrier is a lecithin organogel.

35. The composition of Claim 33 or 34 wherein the form of nicotine is present in the composition in an amount ranging between about 0.001% and about 5.0% (w/w).

36. The composition according to any one of Claims 33 to 35 wherein the form of nicotine is present in the composition in an amount ranging between about 0.05% and about 1.0% (w/w).

37. The composition according to any one of Claims 33 to 36 in dosage unit form wherein the amount of the form of nicotine per dosage unit ranges between about 0.05 mg and about 1.5 mg.

38. The composition of Claim 37 further comprising delta 4,16-androstadien-3-one and/or 1,3,5(10),16-estratetraen-3-ol in an amount ranging between about 0.1 nmoles and about 100 nmoles per dosage unit.

29. The composition of Claim 37 or 38 wherein the amount of delta 4,16-androstadien-3-one and/or 1,3,5(10),16-estratetraen-3-ol per dosage unit ranges between about 0.5 nmoles and about 20 nmoles.

40. The composition according to any one of Claims 1 to 32 wherein the at least one active agent is a central nervous system stimulating agent selected from the group consisting of caffeine, ephedrine, pharmaceutically-acceptable salts thereof and combinations thereof.

41. The composition according to any one of Claims 1 to 32 wherein the at least one active agent is a form of testosterone selected from the group consisting of testosterone, pharmaceutically-acceptable salts thereof and combinations thereof.

42. The composition of Claim 41 wherein the at least one pharmaceutically-acceptable carrier is a lecithin organogel.

43. The composition of Claim 41 or 42 wherein the form of testosterone is present in the composition in an amount ranging between about 0.001% and about 10.0% (w/w).

44. The composition according to any one of Claims 41 to 43 wherein the form of testosterone is present in the composition in an amount ranging between about 0.1% and about 5.0% (w/w).

45. The composition according to any one of Claims 41 to 44 in dosage unit form wherein the amount of the form of testosterone per dosage unit ranges between about 0.05 mg and about 5.0 mg.

46. The composition according to any one of Claims 1 to 32 wherein the at least one active agent is 17ß-estradiol.

47. The composition of Claim 46 wherein the at least one pharmaceutically-acceptable carrier is a lecithin organogel.

48. The composition of Claim 46 or 47 wherein 17ß-estradiol is present in the composition in an amount ranging between about 0.000001% and about 0.01% (w/w).

49. The composition according to any one of Claims 46 to 48 wherein 17ß-estradiol is present in the composition in an amount ranging between about 0.00001% and about 0.0005% (w/w).

50. The composition according to any one of Claims 46 to 49 in dosage unit form wherein the amount of 17ß-estradiol per dosage unit ranges between about 0.05 µg and about 1.0 µg.

51. The composition according to any one of Claims 46 to 50 further comprising progesterone.

52. The composition according to any one of Claims 1 to 32 wherein the at least one active agent is progesterone.

53. The composition according to any one of Claims 1 to 32 wherein the at least one active agent is at least one component of at least one secretion collected from at least one skin surface of at least one donor mammal.

54. The composition of Claim 53 wherein the at least one pharmaceutically-acceptable carrier is a lecithin organogel.

55. The composition of Claim 53 or 54 further comprising at least one additional active agent which has a physiological and/or behavioral effect on at least one recipient mammal.

56. The composition of Claim 55 wherein the at least one additional active agent is selected from the group consisting of delta 4,16-androstadien-3-one, 1,3,5(10),16-estratetraen-3-ol, pharmaceutically acceptable salts thereof and combinations thereof.

57. The composition of Claim 56 in dosage unit form wherein the amount of delta 4,16-androstadien-3-one and/or 1,3,5(10),16-estratetraen-3-ol per dosage unit ranges between about 0.1 nmoles and about 100 nmoles.

58. The composition of Claim 57 wherein the amount of delta 4,16-androstadien-3-one and/or 1,3,5(10),16-estratetraen-3-ol per dosage unit ranges between about 0.5 nmoles and about 20 nmoles.

59. The composition according to any one of Claims 1 to 32 wherein the at least one active agent is selected from the group consisting of delta 4,16-androstadien-3-one, 1,3,5(10),16-estratetraen-3-ol, pharmaceutically acceptable salts thereof and combinations thereof.

60. The composition of Claim 59 wherein the at least one pharmaceutically-acceptable carrier is a lecithin organogel.

61. The composition of Claim 59 or 60 in dosage unit form wherein the amount of delta 4,16-androstadien-3-one and/or 1,3,5(10),16-estratetraen-3-ol per dosage unit ranges between about 0.1 nmoles and about 100 nmoles.

62. The composition of Claim 61 wherein the amount of delta 4,16-androstadien-3-one and/or 1,3,5(10),16-estratetraen-3-ol per dosage unit ranges between about 0.5 nmoles and about 20 nmoles.

63. The composition according to any one of Claims 59 to 62 further comprising at least one additional active agent selected from the group consisting of a narcotic, an opiate, an opioid, an NMDA receptor antagonist and combinations thereof.

64. The composition according to any one of Claims 59 to 62 further comprising a central nervous system stimulating agent selected from the group consisting of caffeine, ephedrine, pharmaceutically-acceptable salts thereof and combinations thereof.

65. The composition according to any one of Claims 59 to 62 further comprising at least one sex hormone.

66. The composition according to any one of Claims 59 to 62 further comprising an anti-depressant agent, a tranquilizer and combinations thereof.

67. Use of the composition according to any one of Claims 1 to 32 to treat and/or prevent a disease and/or condition of a mammal.

68. Use of the composition according to any one of Claims 1 to 32 to diagnose a disease and/or condition of a mammal.

69. Use of the composition according to any one of Claims 1 to 32 to stimulate the brain of a mammal.

70. Use of the composition according to any one of Claims 1 to 32 to initiate and/or modulate at least one of physiology, thoughts, emotions, moods or behavior of a mammal.

71. Use of the composition according to any one of Claims 1 to 32 to decrease the effective dosage amount of the at least one active agent that is required to be administered to a mammal to obtain a desired effect relative to the effective dosage amount of the at least one active agent which would normally be administered by the vascular route to obtain a substantially similar effect.

72. Use of the composition according to any one of Claims 1 to 32 to reduce the risk to a mammal of contracting at least one needle-transmitted communicable disease and/or condition.

73. Use of the composition according to any one of Claims 33 to 39 in at least one of smoking cessation therapy, nicotine replacement therapy or the treatment of smoking withdrawal syndrome.

74. Use of the composition of Claim 40 to improve at least one of performance or learning.

75. Use of the composition according to any one of Claims 41 to 45 as a male contraceptive agent.

76. Use of the composition according to any one of Claims 41 to 45 to increase libido.

77. Use of the composition according to Claims 46 to 50 to treat, prevent or reduce at least one symptom of perimenopause selected from the group consisting of hot flashes, short-term memory loss, fuzzy thinking and combinations thereof.

78. Use of the composition according to Claims 46 to 52 as a female contraceptive agent.

79. Use of the composition according to any one of Claims 53 to 58 to elicit at least one of an energizing effect, an alerting sensation, an increase in sexual arousal and combinations thereof in at least one recipient mammal.

80. Use of the composition according to any one of Claims 53 to 58 for treating, preventing, aborting and/or reducing the severity of acute anxiety attacks with obsessional elements in at least one recipient mammal.

81. Use of the composition according to any one of Claims 53 to 58 for treating insomnia.

82. Use of the composition according to any one of Claims 53 to 58 to elicit at least one pleasurable mood in at least one recipient mammal wherein the at least one pleasurable mood is selected from the group consisting of alerting, sexual arousal, relaxation, energizing, increased creativity, enhanced pleasurable sensations and responses during periods of intimacy and combinations thereof.

83. The use of Claim 82 wherein the at least one donor mammal and the at least one recipient mammal are of opposite sex and are heterosexual.

84. The use of Claim 83 wherein the at least one donor mammal and the at least one recipient mammal are of the same sex and are homosexual.

85. Use of the composition according to any one of Claims 53 to 58 to modulate at least one symptom in at least one female recipient mammal wherein the at least one symptom is associated with at least one syndrome selected from the group consisting of pre-menstrual syndrome, pre-menopausal syndrome, menopausal syndrome, post-menopausal syndrome and combinations thereof and wherein the at least one secretion is collected from at least one donor mammal selected from the group consisting of a male, a female and combinations thereof.

86. Use of the composition according to any one of Claims 53 to 58 to modulate the menstrual cycle of at least one female recipient mammal wherein the at least one donor mammal is selected from the group consisting of a male, a female and combinations thereof.

87. Use of the composition according to any one of Claims 53 to 58 to elicit a sexual arousal response in at least one recipient mammal.

88. Use of the composition according to any one of Claims 59 to 62 to elicit feelings selected from the group consisting of elation, euphoria, stimulation, friendliness, vigor, non-sexual alertness, relaxation, mellowness and combinations thereof.

89. Use of the composition according to any one of Claims 59 to 62 to elicit the emotional and/or behavioral response of alerting in combination with relaxation in a female mammal.

90. Use of the composition of Claim 59 to 62 prior to and/or following stressful situations.

91. Use of the composition of Claim 59 to 62 in the treatment of at least one disease or condition selected from the group consisting of obsessive-compulsive disorder, acute anxiety states and combinations thereof.

92. Use of the composition of Claim 63 to modulate pain states.

93. Use of the composition of Claim 64 to improve at least one of performance or learning.

94. Use of the composition of Claim 64 to counteract the irritability caused by the administration of caffeine alone wherein the central nervous system stimulating agent is a form of caffeine selected from caffeine, a pharmaceutically-acceptable salt thereof and combinations thereof

95. Use of the composition of Claims 65 to enhance libido in a mammal.

96. Use of the composition according to any one of Claims 65 to modulate the emotional effects caused by hormone fluctuations experienced by a mammal having at least one condition selected from the group consisting of pre-menstrual syndrome, andropause and menopause.

97. Use of the composition of Claim 66 to decrease the effective dosage amount of the anti-depressant agent and/or tranquilizer that is required to be administered to a mammal to obtain a desired effect.

98. A method of preparing the composition of Claim 53 wherein the method comprises:

(a) collecting the at least one component of the at least one secretion from the at least one skin surface of the at least one donor mammal,

(b) optionally extracting the at least one component from the collection into a solvent,

(c) optionally purifying the extraction to obtain less than the total complement of components of the at least one secretion,

(d) optionally concentrating the extraction or purification to obtain a concentrated solution of the at least one component,

(e) optionally adding at least one additional active agent to the extraction, purification or concentration, and

(f) mixing the collection, extraction, purification, concentration or combination with the at least one pharmaceutically-acceptable carrier to obtain the composition.

99. The method of Claim 98 wherein the at least one skin surface is selected from the group consisting of the upper lip, at least one of the axillae, the perineum, the inside of at least one of the thighs, the urethra, the vagina, the penis and combinations thereof.

100. The method of Claim 98 or 99 wherein the at least one secretion is collected following intercourse, self-stimulation or physical exercise.

101. The method according to any one of Claims 98 to 100 wherein the collection is accomplished by wiping the at least one skin surface with an absorbent means.

102. The method of Claim 101 wherein the extraction is accomplished by immersing the absorbent means in the solvent.

103. The method according to any one of Claims 98 to 102 wherein the solvent is a lower chain alcohol.

104. The method according to any one of Claims 98 to 103 wherein the at least one additional active agent has a physiological and/or behavioral effect on the brain of a mammal.

105. The method according to any one of Claims 98 to 104 wherein the mixing is accomplished by immersing the absorbent means in the at least one pharmaceutically-acceptable carrier.

106. The method according to any one of Claims 98 to 105 wherein the at least one pharmaceutically-acceptable carrier is a lecithin organogel.

107. Use of at least one active agent in combination with at least one pharmaceutically-acceptable carrier in the manufacture of a composition for the

treatment and/or prevention of a disease and/or condition in a mammal by administering the composition to the nasal mucosa of the mammal, the composition providing for the delivery of the at least one active agent through at least one area of the nasal epithelium to at least one group of nerve fibers, along at least one neural pathway and into the brain of the mammal.

108. Use of at least one active agent in combination with at least one pharmaceutically-acceptable carrier in the manufacture of a composition for the diagnosis of a disease and/or condition in a mammal by administering the composition to the nasal mucosa of the mammal, the composition providing for the delivery of the at least one active agent through at least one area of the nasal epithelium to at least one group of nerve fibers, along at least one neural pathway and into the brain of the mammal.

109. Use of at least one active agent in combination with at least one pharmaceutically-acceptable carrier in the manufacture of a composition for the initiation and/or modulation of at least one of the physiology, behavior, thoughts, moods or emotions of a mammal by administering the composition to the nasal mucosa of the mammal, the composition providing for the delivery of the at least one active agent through at least one area of the nasal epithelium to at least one group of nerve fibers, along at least one neural pathway and into the brain of the mammal.

110. Use of at least one active agent in combination with at least one pharmaceutically-acceptable carrier in the manufacture of a composition for stimulating the brain of a mammal by administering the composition to the nasal mucosa of the mammal, the composition providing for the delivery of the at least one active agent through at least one area of the nasal epithelium to at least one group of nerve fibers, along at least one neural pathway and into the brain of the mammal.

111. Use of at least one active agent in combination with at least one pharmaceutically-acceptable carrier in the manufacture of a composition for decreasing the effective dosage amount of at least one active agent that is required

to be administered to a mammal to obtain a desired effect relative to the effective dosage amount of the at least one active agent which would normally be administered by the vascular route to obtain a substantially similar effect by administering the composition to the nasal mucosa of the mammal, the composition providing for the delivery of the at least one active agent through at least one area of the nasal epithelium to at least one group of nerve fibers, along at least one neural pathway and into the brain of the mammal.

112. Use of at least one active agent in combination with at least one pharmaceutically-acceptable carrier in the manufacture of a composition for reducing the risk to a mammal of contracting at least one needle-transmitted communicable disease and/or condition by administering the composition to the nasal mucosa of the mammal, the composition providing for the delivery of the at least one active agent through at least one area of the nasal epithelium to at least one group of nerve fibers, along at least one neural pathway and into the brain of the mammal.

113. The use according to any one of Claims 107 to 112 wherein the at least one active agent is capable of at least one of delivering itself through the at least one area of the nasal epithelium, delivering itself to the at least one group of nerve fibers, delivering itself along the at least one neural pathway, delivering itself into the brain of the mammal and combinations thereof.

114. The use according to any one of Claims 107 to 113 wherein the amount of the at least one active agent administered is substantially less than the amount of the at least one active agent which would normally be administered to the mammal to be delivered to the brain by the vascular route to achieve a substantially similar effect.

115. The use according to any one of Claims 107 to 114 wherein the at least one active agent is selected from the group consisting of a therapeutic agent, a prophylactic agent, a diagnostic agent, an agent which stimulates the brain of a mammal, an agent which initiates and/or modulates at least one of the

physiology, behavior, thoughts, moods or emotions of a mammal and combinations thereof.

116. The use according to any one of Claims 107 to 115 wherein the at least one active agent is selected from the group consisting of at least one component of at least one secretion collected from at least one skin surface of at least one donor mammal, cholinomimetic agents, central nervous system stimulants, sedatives, narcotics, narcotic antagonists, opioids, opiates, NMDA receptor antagonists, anxiolytic agents, anti-depressant agents, tranquilizers, analgesics, anti-migraine agents, anti-convulsant agents, anti-obsessional agents, anti-psychotic agents, anti-Parkinsonian agents, anti-mania agents, agents for the treatment of eating disorders, agents for the treatment of Alzheimer's Disease, agents for the treatment of attention deficit disorders, agents for the treatment of learning disorders, agents for the treatment of memory disorders, agents for the treatment of cognitive disorders, hormones, hormone releasing factors, pheromones, vomeropherins, agents which affect the autonomic nervous system, appetite-suppressant agents, libido-modulating agents, mood-modulating agents, vitamins, minerals, infective agents, agents which modify the mammalian genome or any of the biological effects (intracellular or extracellular) which result therefrom, vaccines, intracellular modifiers, contraceptive agents, anti-viral agents, anti-bacterial agents, anti-neoplastic agents, anti-parasitic agents, anti-inflammatory agents, anti-fungal agents, hypnotic agents, anti-emetic agents, tranquilizers, diagnostic agents, agents which modify the natural aging process of a mammal, agents for the diagnosis and/or treatment of chemical addictions, agents for the treatment of sleep disorders and combinations thereof.

117. The use of Claim 116 wherein the cholinomimetic agent is selected from the group consisting of nicotine base, pharmaceutically-acceptable salts thereof, metabolites thereof, analogs thereof and combinations thereof.

118. The use of Claim 116 wherein the central nervous system stimulant is selected from the group consisting of caffeine, ephedrine, pharmaceutically-acceptable salts thereof and combinations thereof.

119. The use of Claim 116 wherein the hormone is selected from the group consisting of a sex hormone, analogs thereof, precursors thereof, metabolites thereof and combinations thereof.

120. The use of Claim 116 wherein the sex hormone is selected from the group consisting of an androgen, an estrogen, a progestogen and combinations thereof.

121. The use of Claim 120 wherein:

(a) the androgen is selected from the group consisting of testosterone, pharmaceutically-acceptable salts thereof and combinations thereof;

(b) the estrogen is selected from the group consisting of estradiol, estriol, estrone, pharmaceutically acceptable salts thereof and combinations thereof; and

(c) the progestogen is selected from the group consisting of progesterone, pharmaceutically-acceptable salts thereof and combinations thereof.

122. The use of Claim 121 wherein the estradiol is 17ß-estradiol.

123. The use of Claim 119 wherein the precursor of a sex hormone is selected from the group consisting of delta 4,16-androstadien-3-one, 1,3,5(10),16-estratetraen-3-ol, pharmaceutically acceptable salts thereof and combinations thereof.

124. The use of Claim 116 wherein the hormone is selected from the group consisting of a pituitary hormone, a hypothalamic hormone and combinations thereof.

125. The use of Claim 116 wherein the infective agent is selected from the group consisting of bacteria, viruses and combinations thereof.

126. The use of Claim 116 wherein the hormone releasing factor is selected from the group consisting of a hypothalamic hormone releasing factor, a pituitary hormone releasing factor and combinations thereof.

127. The use of Claim 116 wherein the agent which modifies the mammalian genome is selected from the group consisting of DNA, RNA and combinations thereof.

128. The use of Claim 116 wherein the diagnostic agent is selected from the group consisting of a monoclonal antibody, a polyclonal antibody, a chemical reagent and combinations thereof.

129. The use of Claim 128 wherein the diagnostic agent is labeled with a labeling agent selected from the group consisting of a radioactive agent, an enzymatic agent, a fluorescent agent and combinations thereof.

130. The use of Claim 129 wherein the diagnostic agent is an antibody and is labeled by means of a reaction with a second labeled antibody.

131. The use according to any one of Claims 107 to 130 wherein the at least one pharmaceutically-acceptable carrier facilitates the delivery of the at least one active agent through the at least one area of the nasal epithelium, to the at least one group of nerve fibers, along the at least one neural pathway, and to the at least one brain center of the mammal and combinations thereof.

132. The use according to any one of Claims 107 to 131 wherein the at least one pharmaceutically-acceptable carrier is selected from the group consisting of an oil-water emulsion, a microemulsion, an organogel, phosphatidylcholine, phosphatidylserine, sphingomyelin, a phosphatidylcholine organogel, a lecithin organogel, a lecithin microemulsion, a vesicle, a micelle, a proliposome, a liposome, a soluble synthetic polymer, a block co-polymer micelle, a microsphere, a microsponge and combinations thereof.

133. The use according to any one of Claims 107 to 132 wherein the composition is in a form selected from the group consisting of a liquid, a powder, a spray, an aerosol, drops, a cream, a gel, and an ointment.

134. The use according to any one of Claims 107 to 133 wherein the at least one area of the nasal epithelium is selected from the group consisting of the vomeronasal epithelium, the respiratory epithelium, the lateral nasal epithelium and combinations thereof.

135. The use according to any one of Claims 107 to 134 wherein the vomeronasal epithelium is selected from the group consisting of the nasal epithelium overlying the vomeronasal organ, the nasal epithelium overlying the vomeronasal-terminalis neural pathway, the nasal epithelium proximate thereto and combinations thereof.

136. The use according to any one of Claims 107 to 135 wherein the at least one group of nerve fibers is selected from the group consisting of the vomeronasal-terminalis nerve fibers, the trigeminal nerve fibers, the autonomic nerve fibers and combinations thereof.

137. The use according to any one of Claims 107 to 136 wherein the at least one neural pathway is selected from the group consisting of the vomeronasal-terminalis neural pathway, the trigeminal neural pathway, the autonomic neural pathway and combinations thereof.

138. The use according to any one of Claims 107 to 137 wherein the at least one active agent is transported to the brain via transneuronal anterograde transport, transneuronal retrograde transport and combinations thereof.

139. The use according to any one of Claims 107 to 138 wherein the at least one active agent is delivered to at least one brain center.

140. The use of Claim 139 wherein the at least one brain center is selected from the group consisting of a sexual brain center, a non-sexual brain center and combinations thereof.

141. The use of Claim 139 or 140 wherein the at least one brain center is within the diencephalon area.

142. The use according to any one of Claims 139 to 141 wherein the at least one brain center is selected from the group consisting of the amygdala, the hypothalamus, the cingulate gyrus, the pineal gland, the thalamus, the limbic system, the prefrontal cortex, the temporal cortex and combinations thereof.

143. The use according to any one of Claims 139 to 141 wherein the at least one brain center is involved in at least one of neuroendocrine regulation, modulation of physiology, initiation and/or modulation of thoughts, initiation and/or modulation of emotions, initiation and/or modulation of moods or initiation and/or modulation of behavior.

144. The use according to any one of Claims 107 to 143 wherein the at least one active agent is a form of nicotine selected from the group consisting of nicotine base, pharmaceutically-acceptable salts thereof, metabolites thereof, analogs thereof and combinations thereof.

145. The use of Claim 144 wherein the at least one pharmaceutically-acceptable carrier is a lecithin organogel.

146. The use of Claim 144 or 145 wherein the form of nicotine is present in the composition in an amount ranging between about 0.001% and about 5.0% (w/w).

147. The use according to any one of Claims 144 to 146 wherein the form of nicotine is present in the composition in an amount ranging between about 0.05% and about 1.0% (w/w).

148. The use according to any one of Claims 144 to 147 wherein the composition is in dosage unit form and wherein the amount of the form of nicotine per dosage unit ranges between about 0.05 mg and about 1.5 mg.

149. The use of Claim 148 wherein the composition further comprises delta 4,16-androstadien-3-one and/or 1,3,5(10),16-estratetraen-3-ol in an amount ranging between about 0.1 nmoles and about 100 nmoles per dosage unit.

150. The use of Claim 149 wherein the amount of delta 4,16-androstadien-3-one and/or 1,3,5(10),16-estratetraen-3-ol per dosage unit ranges between about 0.5 nmoles and about 20 nmoles.

151. The use according to any one of Claims 107 to 143 wherein the at least one active agent is a central nervous system stimulating agent selected from the group consisting of caffeine, ephedrine, pharmaceutically-acceptable salts thereof and combinations thereof.

152. The use according to any one of Claims 107 to 143 wherein the at least one active agent is a form of testosterone selected from the group consisting of testosterone, pharmaceutically-acceptable salts thereof and combinations thereof.

153. The use of Claim 152 wherein the at least one pharmaceutically-acceptable carrier is a lecithin organogel.

154. The use of Claim 152 or 153 wherein the form of testosterone is present in the composition in an amount ranging between about 0.001% and about 10.0% (w/w).

155. The use according to any one of Claims 152 to 154 wherein the form of testosterone is present in the composition in an amount ranging between about 0.1% and about 5.0% (w/w).

156. The use according to any one of Claims 152 to 155 in dosage unit form wherein the amount of the form of testosterone per dosage unit ranges between about 0.05 mg and about 5.0 mg.

157. The use according to any one of Claims 107 to 143 wherein the at least one active agent is 17ß-estradiol.

158. The use of Claim 157 wherein the at least one pharmaceutically-acceptable carrier is a lecithin organogel.

159. The use of Claim 157 or 158 wherein 17ß-estradiol is present in the composition in an amount ranging between about 0.000001% and about 0.01% (w/w).

160. The use according to any one of Claims 157 to 159 wherein 17ß-estradiol is present in the composition in an amount ranging between about 0.00001% and about 0.0005% (w/w).

161. The use according to any one of Claims 157 to 160 in dosage unit form wherein the amount of 17ß-estradiol per dosage unit ranges between about 0.05 µg and about 1.0 µg.

162. The use according to any one of Claims 157 to 161 further comprising progesterone.

163. The use according to any one of Claims 107 to 143 wherein the at least one active agent is progesterone.

164. The use according to any one of Claims 107 to 143 wherein the at least one active agent is at least one component of at least one secretion collected from at least one skin surface of at least one donor mammal.

165. The use of Claim 164 wherein the at least one pharmaceutically acceptable carrier is a lecithin organogel.

166. The use of Claim 164 or 165 wherein the composition further comprises at least one additional active agent which has a physiological and/or behavioral effect on at least one recipient mammal.

167. The use of Claim 166 wherein the at least one additional active agent is selected from the group consisting of delta 4,16-androstadien-3-one, 1,3,5(10),16-estratetraen-3-ol, pharmaceutically acceptable salts thereof and combinations thereof.

168. The use of Claim 167 wherein the composition is in dosage unit form and wherein the amount of delta 4,16-androstadien-3-one and/or 1,3,5(10),16-estratetraen-3-ol per dosage unit ranges between about 0.1 nmoles and about 100 nmoles.

169. The use of Claim 168 wherein the amount of delta 4,16-androstadien-3-one and/or 1,3,5(10),16-estratetraen-3-ol per dosage unit ranges between about 0.5 nmoles and about 20 nmoles.

170. The use according to any one of Claims 107 to 143 wherein the at least one active agent is selected from the group consisting of delta 4,16-androstadien-3-one, 1,3,5(10),16-estratetraen-3-ol, pharmaceutically acceptable salts thereof and combinations thereof.

171. The use of Claims 170 wherein the at least one pharmaceutically-acceptable carrier is a lecithin organogel.

172. The use of Claim 170 or 171 wherein the composition is in dosage unit form and wherein the amount of delta 4,16-androstadien-3-one and/or 1,3,5(10),16-estratetraen-3-ol per dosage unit ranges between about 0.1 nmoles and about 100 nmoles.

173. The use of Claim 172 wherein the amount of delta 4,16-androstadien-3-one and/or 1,3,5(10),16-estratetraen-3-ol per dosage unit ranges between about 0.5 nmoles and about 20 nmoles.

174. The use according to any one of Claims 170 to 173 wherein the composition further comprises at least one additional active agent selected from the group consisting of a narcotic, an opiate, an opioid, an NMDA receptor antagonist and combinations thereof.

175. The use according to any one of Claims 170 to 173 wherein the composition further comprises a central nervous system stimulating agent selected from the

group consisting of caffeine, ephedrine, pharmaceutically-acceptable salts thereof and combinations thereof.

176. The use according to any one of Claims 170 to 173 wherein the composition further comprises at least one sex hormone.

177. The use according to any one of Claims 170 to 173 wherein the composition further comprises an anti-depressant agent, a tranquilizer and combinations thereof.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/CA 00/01311

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	claims 1,3,7-11 page 6, line 21 - line 30 ---	1-173
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
16 February 2001	23/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

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Y	claims 1,12,16 ---	1-173
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Y	claims 1-3,19,33,34,40,45,46,68-70 ---	1-173
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